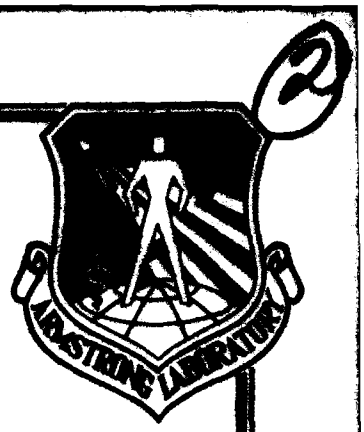

PULSE WAVEFORM AND TRANSCRANIAL DOPPLER ANALYSIS DURING LOWER BODY NEGATIVE PRESSURE

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FOR THE COMMANDER

THOMAS J. MOORE, Chief
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13. ABSTRACT *(Maximum 200 words)*

The use of lower body negative pressure (LBNP) as an acceleration pre-conditioning technique for space applications was investigated. The purpose of this study was to evaluate changes in cephalic blood flow during LBNP. The intent was to see if detection or warning of impending syncope was possible, and to simulate effects which occur under exposure to +Gz. Ten subjects underwent the following LBNP profile while in a standing position: Five minutes of baseline at ambient pressure, followed by increments of -10 mm Hg every three minutes to a minimum of -50 mm Hg. They remained at -50 mm Hg for a maximum of twenty minutes or until presyncopal symptoms occurred. An additional five minutes of post-LBNP baseline data were collected. The analog pulse waveform, obtained from a pulse oximeter sensor located approximately at eye level on the subject's ear lobe. The pulse waveform analysis included pulse area, amplitude, and duration. Other physiological variables included: middle cerebral artery blood flow velocity using transcranial Doppler (TCD) sonography, and oxygen saturation obtained from a pulse oximeter. Six of the ten subjects experienced presyncopal symptoms during the LBNP profile. Significant changes were observed in several variables at the presyncopal endpoint and included: pulse waveform area ($P=0.0048$), pulse waveform amplitude ($P=0.0236$), cerebral artery blood flow velocity ($P=0.0001$), and cerebral artery pulsatility index ($P=0.0357$). In the non-presyncopal group, pulse waveform area ($P=0.0208$), amplitude ($P=0.0070$), and duration ($P=0.0030$) demonstrated significant changes compared to baseline values after exposure to LBNP. Both TCD mean velocity ($P=0.0147$) and pulsatility index ($P=0.0442$) were significantly different between the two groups at the endpoint.

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PREFACE

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INTRODUCTION

Space Shuttle astronauts currently experience gradual onset, relatively long duration, low-Gz exposure during atmospheric re-entry [16, 39]. Given this fact, and the promise of future vehicles such as the National Aerospace Plane (NASP) and Space Station Freedom Assured Crew Return Vehicle (ACRV), medical monitoring systems are an important consideration.

Early symptoms of impending G-induced loss of consciousness (GLOC) could still be a potential problem for low-G exposures if the subject has undergone cardiovascular deconditioning or is hypovolemic. This may be an even greater problem in the future, with the duration of space missions expected to increase. Even without frank GLOC, performance decrements could occur because of decreased cerebral blood flow which might adversely affect a crewmember during a critical time period.

Space shuttle crewmembers currently experience a peak of approximately 1.5 to 1.6 +Gz during re-entry [16, 21, 27, 39]. Although there are no reports of GLOC or presyncope during the reentry phase, one Space Shuttle crewmember has reported using anti-G straining maneuvers during this time period [38].

Anecdotal reports at Armstrong Laboratory, Wright-Patterson Air Force Base (WPAFB) in Dayton, Ohio have demonstrated a change in head-level analog pulse waveform signals obtained from pulse oximeters during exposure of subjects to +Gz on the Dynamic Environment Simulator (DES). This effect is illustrated in Appendix C. Many studies by Wood et al., have previously demonstrated similar results using "ear opacity" techniques during +Gz centrifuge exposure [28, 29, 30, 31, 32].

Recently, there has been great interest in the performance decrement that occurs prior to full recovery after G-induced loss of consciousness (GLOC) [10]. In addition, there is also great interest in developing methods for detecting impending GLOC and giving feedback to the pilot or crewmember, with the intent of warning or initiating an automatic control system until the pilot recovers [10, 28, 29, 30, 31].

This research study was performed to detect any changes in head-level plethysmographic pulse waveform and cerebral blood flow that occur during presyncopal lower body negative pressure (LBNP) exposure. LBNP was used with the intent of simulating +Gz [13, 20], and provided the additional benefit of a stationary experimental environment.

Analog arterial pulse waveform data were obtained from a pulse oximeter of a type commonly used to monitor the oxygen saturation and heart rate of clinical patients. In addition, a means of analyzing the pulse waveform in real-time using a microcomputer was developed for this experiment. Simultaneously, cerebral

artery blood flow was analyzed through the use of transcranial Doppler (TCD) sonography. Ultimately, this research relates to the possibility of using these methods as a physiological feedback, monitoring, or warning device prior to the onset of presyncope caused by a decrease in blood flow to the head [30, 32].

BACKGROUND

Lower Body Negative Pressure (LBNP)

Lower Body Negative Pressure (LBNP) is a method in which the abdomen and legs of a subject are exposed to a negative gauge pressure, causing up to one liter of blood to pool in the lower body [22, 23]. The resulting physiological effects are similar to those occurring during hypovolemic shock, high-G acceleration (+Gz), and orthostasis [26, 23].

The application of negative pressure to the body for scientific or medical purposes was first used in 1841 by Junod, who used it to create a localized hyperemia [26]. Junod also suggested that it could be used prior to invasive surgical procedures, since the syncope it was able to produce was considered a "satisfactory state" prior to invasive procedures [26]. This method attained some success, but interest sharply declined around the turn of the century [26]. In the early 1950's, there was new interest in this procedure among researchers who used it to investigate the response of peripheral resistance vessels to varying ranges of transmural pressures during orthostasis and acceleration [26]. Major interest in LBNP began in the early 1960's when investigators realized that it caused physiological effects similar to those observed during orthostasis and head-up tilt. Aerospace researchers were also interested in spaceflight-related applications of LBNP because the cardiovascular stresses it imposed were independent of gravity [26]. LBNP also simulates central hypovolemia, allowing the study of acute hemorrhage [26].

Since then, LBNP has been extensively utilized in the aerospace medicine field. Presyncopal LBNP involves exposure of the lower one-half of the body to increasingly negative gauge pressure until the subject experiences symptoms of impending syncope. It is used to study the cardiovascular effects of orthostasis and evaluate subjective tolerance. LBNP is used to simulate +Gz in aerospace medicine research [13]. It has also been studied as a potential countermeasure to negative Gz acceleration [3].

Based on heart rate data, Lategola and Trent estimated that -50 mm Hg supine LBNP was considered to be equal to -40 mm Hg seated LBNP [13]. In terms of blood volume and heart rate displacements, a negative pressure of -50 mm Hg of supine LBNP is considered to be equivalent to +2 Gz [14, 15]. Work by Polese et al., has indicated that +2 Gz and -40 mm Hg seated LBNP resulted

in similar changes in heart rate, diastolic blood pressure, and mean arterial pressure [20]. The changes in systolic blood pressure and pulse pressure were more severe with seated LBNP than with +2 Gz [20].

Current experiments on Space Shuttle missions are designed to study the use of LBNP on-orbit as a possible countermeasure to the potentially serious and very common orthostatic intolerance experienced by astronauts after returning to the 1 G environment of the earth. This orthostatic intolerance often occurs despite the use of countermeasures such as fluid loading and G-suits [7].

Transcranial Doppler (TCD)

The use of transcranial Doppler sonography (TCD) to monitor the velocity of blood in the basal cerebral arteries was first reported by Aaslid et al., in 1982 [1]. Prior to that time, Doppler ultrasonography had only been able to record flow velocity in the extracranial arteries. Since 1982, it has been used clinically in neurology and neurosurgery to assess blood flow velocities of the intracranial (basal cerebral) arteries [6]. Transcranial Doppler has proven its usefulness during medical situations such as subarachnoid hemorrhage, intra- and extra-cranial vascular disease, and monitoring during surgical procedures [6]. It has emerged as a reliable technique for assessing both blood flow and cerebral vasoreactivity [12].

The technique is based upon measurement of the Doppler frequency shift of reflected ultrasonic waves after they strike moving red blood cells [6]. The various cerebral arteries each have their own characteristic TCD waveform, depth, location, and flow direction. This allows their unique identification by sonography [19, 37]. Typically, transcranial Doppler devices provide information on mean flow velocity, along with peak systolic and diastolic values [43].

Recent interest in the use of transcranial Doppler in aerospace medicine has included studies of cerebral blood flow during syncope [17], +Gz acceleration [25], and correlation with space adaptation syndrome [2].

Pulse Oximetry [40, 41, 42, 45]

Pulse oximeters are commonly used in clinical medicine to non-invasively measure the arterial oxygen saturation and heart rate of patients. Their operation centers on the ability of the hemoglobin molecule to reversibly bind and release oxygen inside erythrocytes.

Each hemoglobin molecule is able to carry four oxygen molecules

[4]. The entire molecule is called oxyhemoglobin when it is carrying oxygen molecules, and deoxyhemoglobin when it is no longer carrying oxygen (i.e., after release to body tissues). Deoxyhemoglobin and oxyhemoglobin differ in their spectrophotometric properties. This fact forms the basis of operation for most pulse oximeters [41, 42, 45].

In general, the pulse oximeter sensor consists of an emitter and detector combination. The sensor typically uses two light emitting diodes (LEDs) as light sources and a photodiode as a light detector. One LED transmits red light (wavelength of approximately 660 nm) and the other transmits infrared light (wavelength of approximately 940 nm) [41, 42, 45]. The photodiode is placed on the other side of a pulsating vascular bed (typically across a fingertip or ear lobe) and detects the amount of light that passes through the tissue. Oxyhemoglobin absorbs more infrared light and deoxyhemoglobin absorbs more red light [42].

When pulsatile blood flow is not present, the amount of light absorbed will be relatively constant, in the absence of any motion artifact. With each heartbeat, a pulse of blood is propelled past the sensor unit. The inflow of blood will increase the absorption of both infrared and red light, but proportionally more infrared light will be absorbed because the new pulse of blood is particularly high in oxyhemoglobin. The ratio of light absorbed during pulsatile flow to the amount absorbed when pulsatile flow is absent can be calculated. Using a spectrophotometric relationship known as Beer's law, the logarithm of this ratio can be used to determine the oxygen saturation of arterial hemoglobin [41].

The pulse oximeter used in this study is a type commonly used in clinical medicine. It calculates "functional" oxygen saturation, defined as the amount of oxygenated hemoglobin as a percent of the hemoglobin capable of transporting oxygen [41]. Since only two wavelengths are used, only oxygenated and deoxygenated "functional" hemoglobins are measured [41]. Significant amounts of dysfunctional hemoglobins such as carboxyhemoglobin or methemoglobin are not detected. Some instruments measure "fractional oxygen saturation" which is defined as the amount of oxygenated hemoglobin expressed as a percent of total hemoglobin [41]. The calculation of fractional oxygen saturation includes the contribution of dysfunctional hemoglobin molecules [41]. For the purposes of this study, "oxygen saturation" or "SaO_2" refers to the oxygen saturation of functional arterial hemoglobin [42].

In addition to oxygen saturation, pulse oximeters typically display heart rate, which is obtained by analyzing the number of pulses passing by the sensor over a defined interval of time.

Pulse oximeters utilize the principle of plethysmography, defined as "the recording of changes in the size of a part as modified by

blood circulation in it," [45]. An analog output of pulse waveform is generated as each pulse of blood absorbs the light emitted by the infrared and visible light diodes. This causes an increased voltage signal output with increased absorption of light and a decreased voltage with decreased absorption, somewhat resembling a sinusoidal curve as each pulse of blood passes by the sensor. The shape and amplitude of this signal will vary directly with the amount of light absorbed, whether it is due to a change in oxygen saturation, a decreased amount of blood, or a change in distance between the emitter and detector. The distance between the sensor's emitter and detector is considered to be essentially constant during use [36]. By using this plethysmographic technique, the oximeter is able to determine the amplitude, configuration, and frequency of a pulse waveform [45]. An example of the change in analog pulse waveform caused by progressive arterial occlusion with a blood pressure cuff is illustrated in Appendix D.

The following paragraph describes properties of the analog pulse waveform essential to this experiment:

Because pulse oximeters depend on changes in blood volume to calculate saturation, oximeters with a pulse waveform can also provide a non-invasive means of assessing a patient's intravascular volume status. Blood volume changes with each arterial pulse in the same manner as the intraarterial waveform. Therefore, the pulse waveform can be used to assess changes in pressure and hydration (45).

METHODS

Subjects

Eleven healthy volunteer subjects were recruited from the Sustained Acceleration Stress Panel at Wright-Patterson Air Force Base, Ohio. During the experimental run of one particular male subject, there were technical problems with several pieces of equipment, including the pulse oximeter sensor and blood pressure monitor, which resulted in invalid and missing data. This subject was unable to return for a repeat visit and consequently was not included in the final analysis. The remaining ten subjects had the following age characteristics:

TABLE 1. SUBJECT AGE CHARACTERISTICS

	RANGE (years)	MEAN AGE (years)	MEDIAN (years)	S.D. (years)
All Subjects	25-41	30.60	30	5.27
7 males	26-41	32.14	30	5.34

3 females	25-31	27.00	25	3.46

All ten subjects had previous experience with exposure to +Gz on the Dynamic Environment Simulator (DES), a 19 foot radius man-rated centrifuge located at Wright-Patterson Air Force Base. Prior to obtaining informed consent, each subject was given detailed information and instructions concerning the experimental conditions, expected symptoms, and risks.

Materials And Equipment

Two LBNP suits differing in physical size were constructed specifically for this experiment. The two sizes were necessary because of the large variation in physical size of the subjects. The leg sections were constructed out of rigid corrugated PVC tubing which was ten inches in diameter for the small suit and twelve inches in diameter for the large suit. The small suit had flexible knee hinges allowing limited flexion at the knee, which was irrelevant for the purposes of this experiment.

The suit design used was similar to a patented version previously used in LBNP experimentation at Wright-Patterson Air Force Base by Tripp et al., [23]. An outer layer of neoprene-impregnated nylon material formed the pressure seal. Surrounding the waist and groin area, and inserted into each leg section, was a tri-layer of three-dimensional semi-rigid nylon material approximately three millimeters in thickness. This three-dimensional nylon material was essential, as it allowed pressure transfer and equalization between the leg sections of the suit.

Circular neoprene rubber tubes were placed around the abdomen to help contain the suit structures and provide distribution of pressure. Foam padding was placed around the abdomen, upper thigh, and ankles to protect the subject from abrasions and to prevent the suit material from being pulled inside of the leg sections. Since the feet were not surrounded by the hard shell of PVC tubing, the subjects wore either military boots, athletic shoes or fiberglass casting material boots to protect their feet from the pressure. The large suit used a section of vinyl fisherman's waders to provide the outer foot seal. The small suit used an extension of the outer nylon/neoprene covering to provide the foot seal. The abdominal seal was accomplished by placing a superior extension of the outer nylon/neoprene material directly against the skin and securing it in place with an elastic bandage. One anterior thigh section contained a one-inch pressure evacuation port. A pressure sensing port was located on the opposite anterior thigh section. One-inch diameter reinforced hose connected the suit to a shop vacuum source.

The vacuum source for the LBNP suit was a one-horsepower shop vacuum ("Clements Cadillac Shop-Vac, Model 14, Wet or Dry"). The AC line voltage of this vacuum was controlled using a Variac (rheostat) controller. This allowed fine adjustment of the motor

speed, which regulated the amount of vacuum suction and, ultimately, the suit pressure.
The LBNP suit was connected to the vacuum source by one inch diameter reinforced tubing. A second port on the suit was used to monitor the negative pressure level.

Continuous monitoring of suit pressure was accomplished with a dedicated pressure transducer, which converted aneroid pressure information to an analog voltage. The output of this device was connected to the microcomputer discussed below and converted to digital form. In addition, the digital pressure output was calibrated to a standard aneroid analog barometer which was connected in-line with the pressure monitoring port at the beginning of each experiment. Both pressure gauges were monitored throughout each experimental run. To ensure accurate pressure readings, the pressure sensing port and vacuum port were on opposite legs of the LBNP suit.

The investigators and subjects each had separate "abort" switches immediately accessible throughout the experimental run. These consisted of a switch on the Variac controller and a switch on a multi-outlet strip.

Continuous ECG recording was accomplished using disposable electrodes in a standard Einthoven Lead II configuration. The ECG monitor used was a Hewlett-Packard model 78304A with memory ("trickle-down") capability. A standard paper strip-chart recorder was attached in-line to allow hard-copy output of ECG signals on demand.

An additional six-channel strip chart recorder was connected in line with the appropriate signals, to allow hard copy output of suit pressure, ECG, TCD waveform, and pulse waveform.

A Criticare model 503 pulse oximeter was used in conjunction with a Criticare model 560 interface module to allow output of analog signals. The pulse oximeter sensor unit consisted of visible and infrared light emitting diodes and a photodiode detector that was mounted on a plastic clip padded with foam. This sensor is illustrated in Appendix G. The interface module provided continuous oxygen saturation values and analog output of the plethysmographic pulse waveform. The Criticare model 503 does not recalibrate once the initial signal is found (unless the signal is lost and the sensor repositioned) as do certain other brands of pulse oximeters. It provides a "non-gained" waveform output [45]. This quality proved to be essential in allowing detection and analysis of relative changes in the pulse waveform signal shape over time.

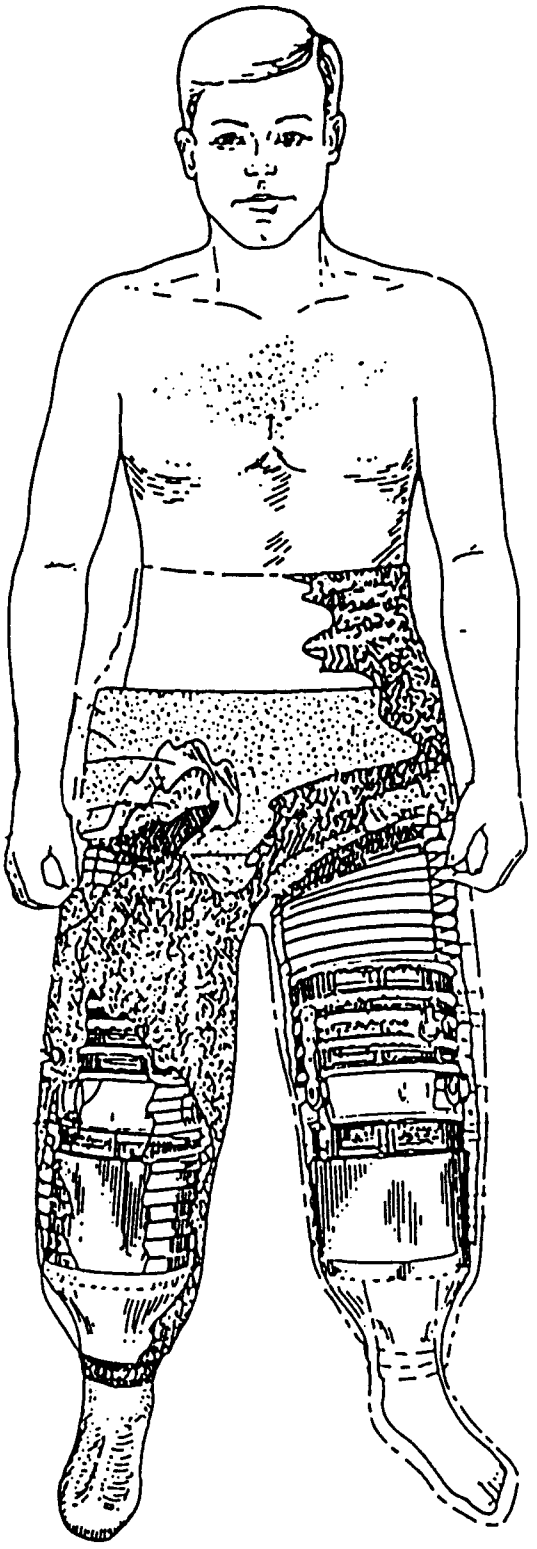


FIGURE 1. LINE DRAWING OF SUBJECT IN LBNP SUIT

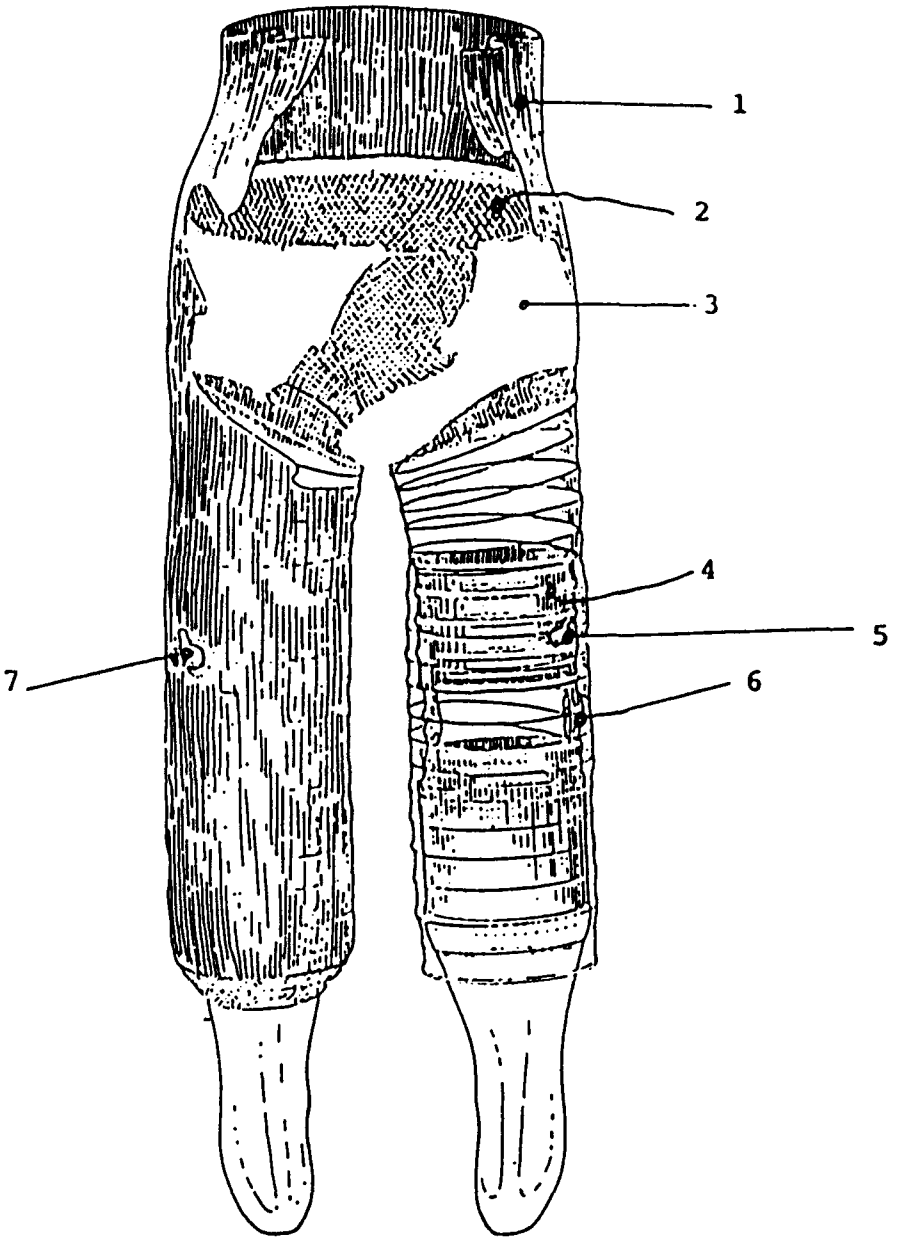


FIGURE 2. ILLUSTRATION OF LBNP SUIT CONSTRUCTION

LEGEND TO SUIT DIAGRAM IN FIGURE 2:
1 = Outer covering of neoprene-impregnated nylon material
2 = Inner layer of semi-rigid 3-dimensional nylon material
3 = Protective foam cushioning
4 = PVC tubing (hard shell) surrounding legs of subject
5 = Suit Evacuation Port
6 = Flexible metal knee hinge (small suit only)
7 = Pressure sensing port (5 & 7 are reversed in the large suit)

The transcranial Doppler (TCD) unit was an EME model TC2-64B Multifrequency Transcranial Doppler unit. This included a transducer probe and velcro head strap unit. The 2 MHz operating mode was utilized. The head strap used provided excellent signal stability. This unit provided continuous output of both real-time and mean cerebral blood flow velocity in centimeters per second along with Gosling's Pulsatility Index (P.I.) [12, 19, 43], defined as:

$$P.I. = (V_S - V_D)/(V_M)$$

V_S = peak systolic velocity
V_D = end diastolic velocity
V_M = time-mean velocity

The Pulsatility Index is a measure of cerebral vasoreactivity. It increases with arteriolar vasoconstriction and decreases with arteriolar vasodilation distal to the insonation point [11, 18].

A Nellcor, Inc. N-CAT model N-500 continuous blood pressure monitoring device was used. This unit provided beat-to-beat blood pressure (systolic, mean, diastolic) and heart rate information obtained from a tonometric sensor placed over the radial artery of the wrist. In addition, it continuously calibrated itself using a standard oscillometric blood pressure cuff on the opposite arm at predefined intervals. The recalibration interval was normally set at four minutes, but was operator selectable if deemed necessary. In addition, auto-recalibration occurred if discrepancies between the tonometric sensor values and the oscillometric cuff were present. During the recalibration mode (either operator selected or automatic), the data output was temporarily suspended until the instrument finished recalibrating.

A serial RS-232 output port on the Nellcor N-CAT model N-500 unit distributed the heart rate and blood pressure information to the computer described in the next paragraph.

A modified Sanyo 80286 12 MHz microcomputer with an 80287 math co-processor was utilized as the main platform. A Willow Peripherals video card with NTSC video capabilities provided the necessary video output, and a National Instruments multifunction I/O board (model Lab-PC) with analog-to-digital conversion capability allowed computer input of the analog signals from the pulse oximeter (oxygen saturation, pulse waveform) and analog pressure gauge. The computer's RS-232 serial port was used to receive information from the Nellcor N-500 blood pressure unit.

The signal from the EME TC-64B transcranial Doppler (TCD) device

was displayed on a built-in cathode ray tube (CRT), which was continuously imaged by a remote video camera unit. The computer monitor display and TCD camera signal, illustrated in Appendices A and B, were combined and displayed onto a separate screen using a Shintron Chromatic model 370 video special-effects generator system. This combined signal was simultaneously recorded on a standard VHS video cassette recorder, providing continuous recording of the digital and analog displays (computer monitor and transcranial Doppler CRT).

A computer program was developed, written, and compiled in the Microsoft Quick C™ language to continuously monitor, display, analyze, and record the confluence of digital and analog data being generated in real-time. The plethysmographic pulse waveform was continuously displayed and analyzed by an area-under-the-curve algorithm. In addition, pulse duration and amplitude were calculated. The pulse waveform was sampled in real-time at 100 Hz in order to determine the area, amplitude, and duration. Data samples were recorded by the computer at one-second intervals throughout the experiment and ultimately saved on a hard disk drive. After the experiment, the data were backed up onto 5.25" floppy disks.

All persons in the experimental environment (including subjects) wore standard disposable foam E-A-R™ plugs for hearing protection because the vacuum source generated more than 74 dB of noise.

Experimental Design

This research took place in April and May of 1992 at Wright-Patterson Air Force Base. It was conducted in two phases, requiring a total of two visits by each subject. The first was called the "training phase", which involved familiarization of the subject with the experiment and a trial run to determine LBNP tolerance. This also helped to reduce anxiety during the actual experimental run. During the "training phase", a standard F-4 Phantom aircraft seat (12 degree seat-back-angle from vertical) was utilized.

Since all ten subjects successfully completed the "training phase" profile and reached a minimum of -50 mm Hg of LBNP without presyncopal symptoms, all were allowed to proceed to the "experimental phase". This involved exposure to LBNP while in a standing position, which increased the pooling effect of LBNP due to the increased influence of gravity.

The "experimental phase" was the actual test and data collection run. It was conducted identically to the "training phase", except that the subject was in a standing position. In addition, the full negative pressure profile was followed until the subject experienced presyncopal symptoms or the maximum time interval was

reached. There was a minimum of three days between the "training phase" and "experimental phase" for each subject.
No attempt was made to control diet or fluid intake prior to the experiment. Subjects were asked to maintain their regular dietary and exercise regimens prior to the study. Informed verbal and written consent was obtained from each subject. To protect their skin from abrasions, each subject wore either a flight suit or long underwear inside of the LBNP suit.

Foam padding was placed around the ankles to provide protection from the inside hard shell of the suit rubbing the subjects ankles. The padding also prevented damage to the outer covering material while at negative pressure by preventing the suit material from being pulled up into the leg sections. The subject donned the appropriately sized suit while either wearing shoes or molded fiberglass casting material "foot protectors." These fiberglass boots were heavily padded on the sole with foam and a sorbothane™ insert. A three-dimensional semi-rigid nylon material was wrapped around the waist area and inserted into each leg section from the top down, providing a means to equalize the pressure between leg sections. Foam padding was inserted into the leg sections after being wrapped around the waist area and thigh to provide protection for the subject and the suit material. Circular neoprene rubber tubes were placed around the subject's waist inside of the outer covering to hold the three-dimensional nylon material in place and to provide a small amount of pressure distribution. The waist seal was accomplished by placing the neoprene-impregnated nylon material (which was the external layer of the entire suit) directly against the skin, followed by an elastic bandage wrap. The seal was located just above the level of the iliac crests bilaterally.

ECG electrodes were placed in a standard Einthoven Lead II configuration, and a rhythm strip was obtained. Foam ear plugs were placed in both ears. The optimal positions for both the TCD probe and ear clip (pulse oximeter sensor) were located. Prior to placement of the ear clip, the ear was cleansed with an alcohol pad. All reasonable attempts were made to locate the best middle cerebral artery waveform with the TCD probe. The TCD insonation site utilized the "transtemporal approach" [19], with the probe placed immediately above the zygomatic arch of the temporal bone. If definite identification of the middle cerebral artery was not possible, the maximum obtainable velocity signal was used. The TCD probe was secured in place on the subject's head using a velcro head mount which provided excellent stability. The Nellcor tonometric blood pressure sensor assembly was placed on the wrist and forearm of the right hand and the oscillometric cuff placed on the left upper arm. The blood pressure sensor and cuff heights were adjusted to be approximately at heart level. The appropriate evacuation hose and pressure port tubing was attached and secured in place.

After all instruments were in position, the subject was asked to

assume a standing position. All instruments were then monitored and recalibrated or repositioned if necessary. Appropriate adjustments were made to the computer program parameters to allow appropriate tracking of the pulse waveform. This consisted of setting the "maximum beats per minute" parameter to within 10-20 beats of the subject's baseline heart rate, allowing proper synchronization of the computer program with the subject's pulse waveform.

After appropriate examination and authorization by the medical monitor, the experiment was started. This consisted of the following pressure profile:

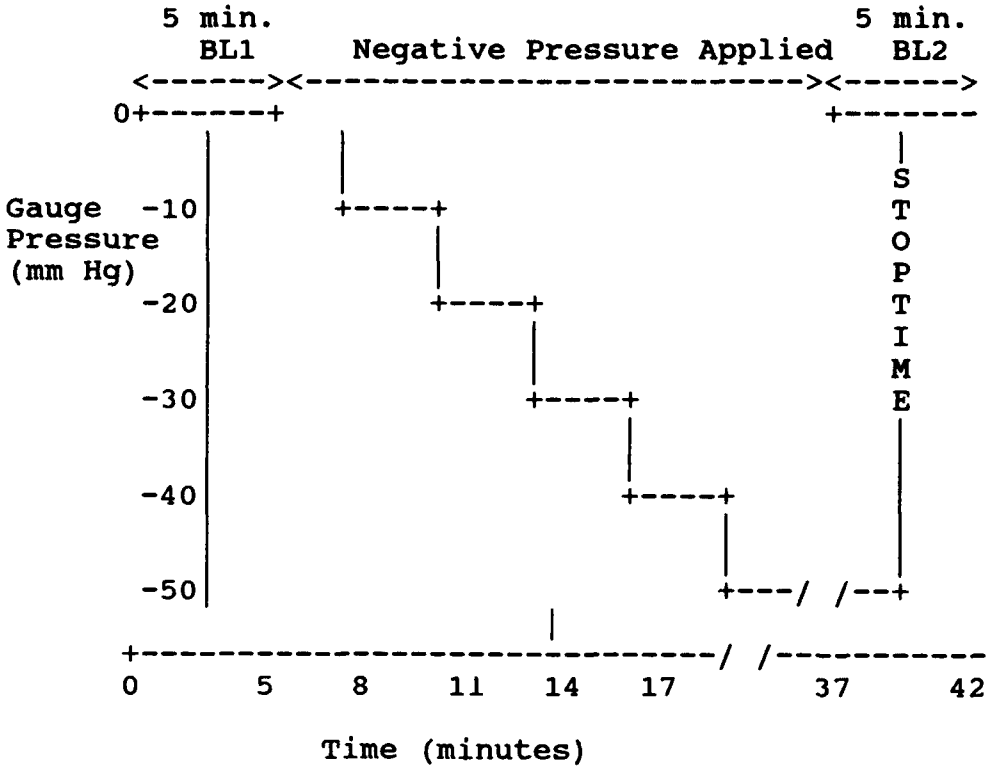


FIGURE 3. LBNP EXPERIMENTAL PROFILE

ABBREVIATIONS USED IN FIGURE 3:
BL1 = Baseline 1
BL2 = Baseline 2
STOPTIME = Experimental Endpoint (maximum 37 minutes)
mm Hg = millimeters of mercury

The first five minutes at ambient pressure (zero mm Hg gauge pressure) were considered "baseline" data. The LBNP profile continued until the subject experienced presyncopal symptoms, requested to stop for any reason, medical profile termination criteria were met, the maximum time interval was reached, or by

request of the experimenters or medical monitor. Each subject was observed by a physician throughout the experiment. The following medical LBNP termination criteria, slightly modified from those originally developed at the Johnson Space Center in Houston, Texas [35], were utilized during this research:

1) Sudden decrease in systolic blood pressure > 25 mm Hg per minute, or decrease in diastolic blood pressure > 15 mm Hg per minute.

2) Sudden decrease in heart rate > 15 beats per minute.

3) Subject nausea, clammy skin, profuse sweating, or pallor of the skin.

4) Subject request for any reason.

5) Systolic blood pressure < 70 mm Hg.

6) Any significant cardiac arrhythmias/dysrhythmias, including bradyarrhythmias, tachyarrhythmias, or heart block.

7) Premature Ventricular Complexes (PVC's) meeting any of the following criteria: 6 or more PVC's per minute, R on T phenomenon, closely coupled PVC's, couplets, runs, or multifocal PVC's.

8) Heart rate (H.R.) greater than 90% of the estimated maximum as determined by the formula: Maximum H.R. = (220 - Age)

9) Loss of ECG signal for any reason.

FIGURE 4. MEDICAL CRITERIA FOR TERMINATING LBNP TEST [35]

The medical criteria were interpreted by the medical monitor(s) on a real-time basis, and consideration was given to the current condition of the subject, trends of the measured physiological variables, and the limitations and idiosyncracies of the monitoring equipment (such as motion artifact, recalibration, sensor drift, etc.).

After the negative pressure was discontinued, an additional five minutes of post-LBNP baseline data were collected. If the subject was presyncopal, he/she was placed in a seated position. If the subject endured the entire profile, he/she remained in a standing position for these five minutes.

After the five minutes of additional data were collected, the instruments were turned off and removed in the reverse manner of how they were placed. During the entire experiment, any subjective symptoms were recorded and the time of occurrence

noted.

Presyncopal subjects were questioned about the nature of their symptoms and the reason for aborting the run. After removal of the suit, the subject was evaluated by the medical monitor and allowed to leave.

Data Collection And Analysis

Data were recorded by several methods including microcomputer disk and VHS videotape. In addition, hard copy strip charts were obtained as needed for ECG, TCD waveform, suit pressure, and pulse waveform.

The microcomputer recorded data on a hard disk drive in the following format at one-second intervals: (sample data is shown in figure 5.).

Subject:_____ Run: _____
Comment:

Ev	Time	SaO2	Suit	Area	Ampl.	Dur.	Stat	Syst	Mean	Dias	Rate
0	00:00	99.80	0.30	5.10	0.13	550	1	120	94	81	88
0	00:01	99.70	-5.60	5.08	0.11	560	1	125	97	83	90
1	00:02	99.80	-8.70	5.09	0.10	560	0	125	97	84	90
1	00:03	99.80	-9.89	5.05	0.11	565	1	124	98	85	92

FIGURE 5. COMPUTER DATA FILE FORMAT

The folowing describes the meaning of each column and abbreviation used in Figure 5.

DESCRIPTION OF COLUMNS IN FIGURE 5:

Ev = optional Event marker (0, 1, 2, etc.)
Time = time since start of experiment in minutes/seconds
SaO_2 = oxygen saturation in percent (from pulse oximeter).
Suit = suit gauge pressure in millimeters of mercury
Area = area under the SaO_2 pulsatile signal, defined as the sum of all voltage readings made during a measured pulse (sampled at 100 Hertz), with the voltage waveform "area" under the pulse's minimum value removed. Since pulse signals were not synchronized with the 1 second data recording interval, this represented the latest completed pulse. This area will vary among subjects, as it depends on physical positioning of the sensor. Pulse waveforms of differing area can be obtained by simply placing the

sensor in a new physical location. It is, however, stable for any given subject assuming no change in sensor position or motion artifact. It is not comparable between subjects except as a percentage change.

Ampl = the measured peak voltage value minus the measured minimum voltage of the latest completed pulse. Like the pulse area, it is dependent upon sensor position and not comparable between subjects except as a percentage change. It is, however, stable for any given subject.

Dur = duration, in milliseconds, of the latest perceived SaO2 pulse. This value is inversely related to the subject's heart

Stat = Nellcor blood pressure unit status field (-1 = error, 0 =no new data, 1 = new data)

Syst = systolic blood pressure in mm Hg

Mean = mean blood pressure in mm Hg

Dias = diastolic blood pressure in mm Hg

Rate = heart rate in beats per minute

The EME Transcranial Doppler unit that was used did not allow direct input of data into the computer (although an upgrade kit is available from EME for this purpose). As a result, the CRT display was imaged with a video camera. This image was merged with the computer display onto a split screen by the video special effects generator unit. The combined computer/TCD screens were then recorded on a standard VHS video cassette recorder. These screens are illustrated in Appendices A and B.

The TCD data included sensor signal depth in millimeters, mean time averaged blood flow velocity in centimeters per second, Pulsatility Index, and a real-time display and audio of each cerebral pulse envelope. After the experiment was completed, the TCD data were manually transcribed from the VHS videotape into a computer data file for subsequent analysis. This TCD data file was in the following format:

Time	Mean	PI	
00:00	45.3	0.65	
00:05	47.3	0.70	
00:09	40.2	1.01	etc.

FIGURE 6. TCD DATA FILE FORMAT

DESCRIPTION OF COLUMNS IN FIGURE 6:

Time = time since start of experiment in min/sec

Mean = mean cerebral flow velocity over one screen refresh interval (approximately 4.5 seconds)

PI = Pulsatility Index, defined as $(V_S-V_D)/(V_M)$ where V_S, V_D and V_M are the peak systolic, end diastolic and time-mean velocities, respectively [12, 43]

The pulse oximeter data presented additional challenges in analysis. The pulse oximeter sensor was extremely sensitive to motion artifact, due to its physical location and nature of measurement. Despite all efforts, it was impossible to completely eliminate motion artifact from the data (due to subject head motion, verbalization, etc.). In addition, the computer program was designed to be extremely sensitive and sample the data at 100 Hz in order to provide the highest possible accuracy in calculating the area under the pulse waveform. Unfortunately, this also created a problem in that minor fluctuations of voltage levels were occasionally incorrectly interpreted as the start of a new pulse. This comprised only a very small amount of the actual data collected.

If the pulse was not being correctly tracked, it was clearly evident on the real-time computer display and documented on the videotaped copy of the entire experiment. If the tracking problem was severe, the operator could manually adjust a synchronization parameter to again regain proper waveform tracking. The analog pulse waveform signal was continuously displayed and monitored throughout the experiment, and the computer program placed vertical lines where it currently defined the beginning and end of a pulse, as outlined below:

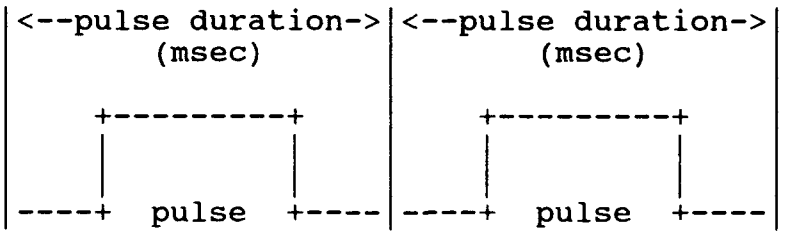


FIGURE 7. DESCRIPTION OF PULSE WAVEFORM

(Note: Appendices C and D illustrate actual pulse waveforms)

The Nellcor N-500 data output included a "Status Byte", which was a code that described the current data being sent. Based on this value, the data were either accepted or discarded according to the following criteria:

Nellcor Data Discard Criteria

If STATUS byte is 0 or -1 , then discard SYST/MEAN/DIAS/RATE information of current line.

If STATUS byte is 1, current data are "new data."

JUSTIFICATION: "0" is defined by Nellcor as "No new data". "-1" is defined as an "Error condition". These codes are sent during the normal data transmission cycle.

The NELLCOR blood pressure unit had an auto-recalibration mode which could not be turned off. As a result, the unit occasionally recalibrated during data collection periods, causing gaps of heart rate and blood pressure information of up to one minute. This information gap was even longer if the signal at the wrist was lost, requiring manual repositioning of the sensor.

The pulse waveform data were susceptible to motion artifact and occasional incorrect sensing during the experiment. Fortunately, this occurrence only comprised a small amount of the total data but did cause several areas of artifactual figures.

Examples of generating incorrect pulse waveform data

Motion artifact occasionally caused the computer program to miss the actual endpoint of the current pulse, creating an artificially large "perceived pulse" having more than twice the duration and area of the most recent pulse.

Motion artifact occasionally caused "spikes" in the pulse waveform voltages, causing the computer to interpret that the end of a pulse had been reached and therefore creating an artificially small "perceived" pulse of extremely small duration and/or area (temporarily).

Temporary loss of the sensor signal due to motion artifact occasionally caused the sudden onset of an extremely small pulse amplitude and/or impossibly low oxygen saturation (for example 50%). This resolved upon discontinuation of motion, again allowing proper synchronization with the pulse signal.

RESULTS

Results of LBNP Profile

All ten subjects completed the seated "training phase" uneventfully and without presyncopal symptoms. This involved, at minimum, reaching the maximum level of -50 mm Hg of LBNP. During the experimental (data collection) phase, subject 05 became presyncopal before the onset of any pressure and before any data were recorded. This subject repeated the experiment approximately one week later and had presyncopal symptoms after application of the normal LBNP pressure profile.

Of the ten subjects who participated in the experimental phase (standing LBNP), six developed presyncopal symptoms. Four of the ten subjects endured the entire 42 minute profile without presyncopal symptoms. In the group of six presyncopal subjects, three were male and three were female. The most common non-presyncopal complaints were foot discomfort, fatigue from standing, and boredom.

All experimental runs that were aborted due to presyncopal symptoms were stopped by subject request. The most common presyncopal symptoms included: stomach awareness, mild nausea, lightheadedness, sensation of impending syncope, hot/cold flashes, feeling cold & "clammy", and sweating.

A difference in LBNP tolerance was noticed between males and females in this experiment. Since there were very few subjects and hydration status was not controlled, no attempt was made to analyze this difference. All three female subjects became presyncopal. Two of the three females became presyncopal at -40 mm Hg, before reaching the maximum negative pressure level. Only three of the seven males experienced presyncopal symptoms. All three of the presyncopal males reached the maximum level of -50 mm Hg before experiencing presyncopal symptoms. Previous work by Frey et al., demonstrated no qualitative differences in cardiovascular responses to LBNP between men and women [8, 9], so these observations were not felt to be significant.

During the experimental run of subject 06, a technical problem occurred with the pulse oximeter sensor, causing erroneous data just prior to the experimental endpoint. It is believed that a positional change in the physical location of the pulse oximeter sensor occurred, which caused a sudden, extremely large, and grossly abnormal increase in pulse waveform area and amplitude prior to discontinuation of pressure. This abnormality is clearly documented on the videotape and computer data file, and did not occur in any of the other subjects. This sudden increase was inconsistent with physiological expectations and the TCD data. Consequently, the following statistical analysis excludes the pulse oximeter data obtained for subject 06. Since the TCD data for subject 06 were not affected, they are included in the statistical analysis. The actual data from Subject 06 are illustrated in Appendix M.

Subjective Reports of Similarity To +Gz

With respect to symptoms they experienced, three of the six presyncopal subjects (subjects 02, 05, and 10) spontaneously reported similarity to +Gz exposure after completing their experimental run.

The following table summarizes the results of the LBNP profile:

TABLE 2. LIST OF SUBJECTS AND RESULTS OF LBNP PROFILES

SUBJECT ID	AGE	PRE-SYNCOPE?	STOP-TIME	SYMPTOMS EXPERIENCED BY SUBJECT
01	38	YES	27:28	mild nausea, cold, clammy, short of breath, lightheaded, feeling of impending syncope
02	31	YES	20:16	stomach awareness, nausea, sweaty, faint/lightheaded
03	31	NO	37:02	foot pain, brief nausea (mild)
04	30	NO	37:00	pressure on feet, legs feeling "heavy"
05	25	YES	15:27	stomach awareness, hot flash, very faint, near-syncope, visual dimming
06	25	YES	15:17	mild nausea, cold, sweating, lightheaded, near-syncope
07	30	NO	37:02	brief stomach awareness, sweating
08	41	NO	37:00	foot discomfort, boredom
09	29	YES	36:01	mild nausea, sweaty, "clammy" lightheaded, short of breath, fatigue
10	26	YES	24:58	disoriented, fatigue, anxiety, high workload, lightheaded, sweaty, felt impending syncope and asked to stop

Note:
STOPTIME is in minutes/seconds and represents the point at which the LBNP profile was discontinued. This was due to subject request, medical termination criteria, or achieving the full profile without presyncopal symptoms. (Please refer to Figure 3 if necessary)

Statistical Results

For all subjects, the physiological variables were compared in the following manner:

BL1 VALUE = The median (pulse area, amplitude, duration), minimum (SaO_2, TCD mean velocity) or maximum (Pulsatility Index) value of the last 15 seconds of BASELINE 1.

STOP VALUE = The median (pulse area, amplitude, duration), minimum (SaO_2, TCD mean velocity) or maximum (Pulsatility Index) value of the 15 seconds prior to STOPTIME.

BL2 VALUE = The median (pulse area, amplitude, duration), minimum (SaO_2, TCD mean velocity) or maximum (Pulsatility Index) value of the last 15 seconds of BASELINE 2.

All six physiological variables were analyzed as a percent change from Baseline 1. For ease of interpretation, the plots which follow are scaled as a percent of Baseline 1 (i.e. Baseline 1 represents 100%). Using the percentage change from Baseline 1 (as opposed to the actual value) eliminated erroneous comparisons of values. Otherwise, a pulse area change from 9 to 7 would have been similarly interpreted as a change from 3 to 1 (i.e. difference of 2 in both cases but a large difference in percent change between them).

Because the pulse oximeter data had occasional motion artifact which would cause extreme values, the median of each 15 second sampling period for pulse area, amplitude, and duration was used instead of the mean. As a measure of central tendency, the median is less sensitive to extreme values than the mean.

For SaO_2 and TCD mean flow velocity, the minimum value of the 15 second sampling period was used because these variables remained stable throughout the profile, only to decrease near the endpoint. For Pulsatility Index, the maximum value of this 15 second sampling period was used because the nature of the pulsatility index was to remain stable until shortly before endpoint, at which time it tended to markedly increase.

Note that TCD flow velocity and pulsatility index already represented a mean value, as previously discussed. SaO_2 similarly remained very stable during most of the profile, only to sharply decrease in several subjects just prior to the experimental endpoint.

TABLE 3. NULL AND ALTERNATE HYPOTHESES

Null Hypothesis H_{01}:   The percent change from Baseline 1 to STOPTIME = 0   Alternate Hypothesis H_{A1}:   The percent change from Baseline 1 to STOPTIME 0
Null Hypothesis H_{02}:   The percent change from Baseline 1 to Baseline 2 = 0   Alternate Hypothesis H_{A2}:   The percent change from Baseline 1 to Baseline 2 0
Null Hypothesis H_{03}:   The percent change between groups at STOPTIME = 0   Alternate Hypothesis H_{A3}:   The percent change between groups at STOPTIME 0

The Student's t-test was used to determine the significance of percent change from Baseline 1. Each of the resulting t-tests used p = 0.05. In addition, a two-sample t-test with p = 0.05 was used to compare the percent change from Baseline 1 between the presyncopal and non-presyncopal groups at STOPTIME.

Because of the nature of this approach and the relatively small sample sizes (N = 4, 5, or 6), the results were cautiously interpreted.

Table 4 shows the p-values calculated using percent change from Baseline 1 (BL1) for each physiological variable.

TABLE 4. COMPARISONS WITHIN GROUPS (P-VALUES):

		NON-PRESYNCOPAL GROUP		PRESYNCOPAL GROUP	
Variable	Comparison	P-Value	Mean %	P-Value	Mean %
AREA	BL1 to STOP	.0208	-56.86%	.0048	-44.00%
	BL1 to BL2	.0100	-38.33%	.6997	+13.60%
AMPLITUDE	BL1 to STOP	.0280	-53.75%	.0236	-38.27%
	BL1 to BL2	.0070	-46.12%	.5716	-13.49%
DURATION	BL1 to STOP	.0030	-19.62%	.3145	-11.48%
	BL1 to BL2	.8768	-0.91%	.0020	+23.72%
SaO_2	BL1 to STOP	.3910	-0.69%	.0757	-5.38%
	BL1 to BL2	.3910	-0.06%	.3739	-0.24%
TCD MEAN VELOCITY	BL1 to STOP	.0727	-16.00%	.0001	-35.61%
	BL1 to BL2	.3027	-6.75%	.6776	-1.76%
P.I.	BL1 to STOP	.4668	-5.89%	.0357	+114.24%
	BL1 to BL2	.0413	-20.83%	.6353	+2.99%

Notes:
BL1 = Baseline 1
STOP = STOPTIME (experimental endpoint)
BL2 = Baseline 2

P.I. = Pulsatility Index
SaO_2 = Oxygen Saturation

N=4 for the non-presyncopal group
N=5 for the presyncopal group: AREA, AMPLITUDE, DURATION, SaO2
N=6 for the presyncopal group: TCD MEAN VELOCITY, P.I.
Mean% = mean change in percent for indicated comparison.

Example: For AREA, the mean for the non-presyncopal group at STOPTIME was 56.86% less than the value at Baseline 1.

Table 5 shows the p-values obtained from a two-sample t-test by comparing the percent change from Baseline 1 at STOPTIME between the presyncopal and non-presyncopal groups.

TABLE 5. COMPARISONS BETWEEN GROUPS AT STOPTIME:

Variable	P-Value	Mean %	Pooled S.D.
AREA	.3957	+12.87%	21.20%
AMPLITUDE	.3920	+15.48%	25.30%
DURATION	.5015	+8.14%	17.13%
SaO_2	.1177	-4.69%	3.92%
TCD MEAN VELOCITY	.0147	-19.61%	9.80%
P.I.	.0442	+120.12%	78.04%

Notes:

N=4 for the non-presyncopal group
N=5 for the presyncopal group: AREA, AMPLITUDE, DURATION, SaO_2
N=6 for the presyncopal group: TCD MEAN VELOCITY, P.I.

P.I. = Pulsatility Index
S.D. = Standard Deviation
SaO2 = Oxygen Saturation
Mean% = mean change in percent, between groups, of the variable at STOPTIME

Example: At STOPTIME, for the variable AREA, the group mean for the presyncopal group was 12.87% greater than the group mean for the non-presyncopal group.

Graphs: Two-Minute Window Around STOPTIME

The graphs in this section (Figures 8-10) demonstrate the sudden changes in SaO_2, TCD mean velocity, and Pulsatility Index which occurred just prior to the presyncopal endpoint (STOPTIME). A two-minute window surrounding STOPTIME is displayed for each subject. Only TCD mean velocity, Pulsatility Index, and SaO_2 are shown because the other three variables (Pulse Area, Amplitude, and Duration) did not demonstrate any sudden changes during this time period.

Oxygen Saturation

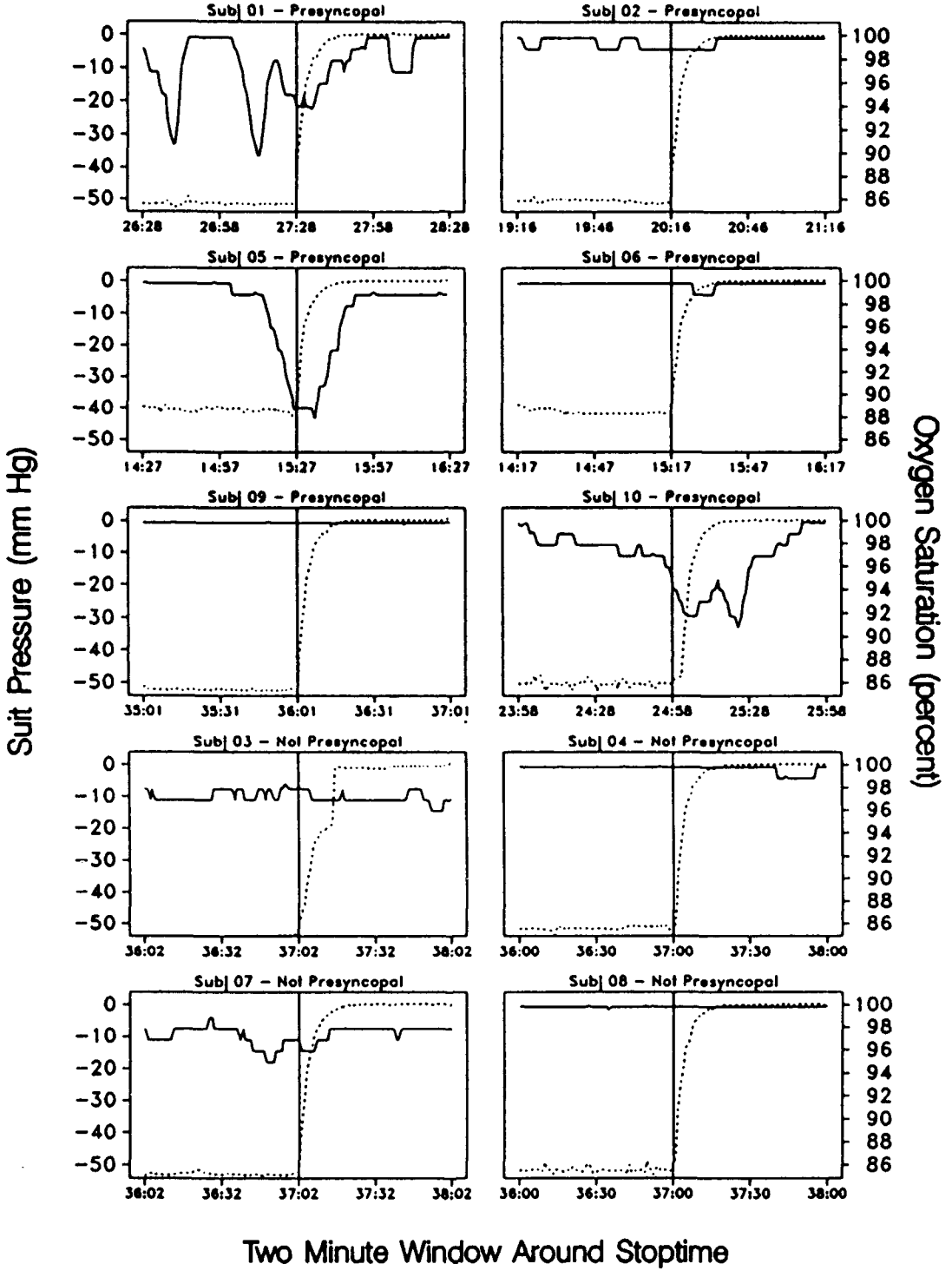


FIGURE 8.

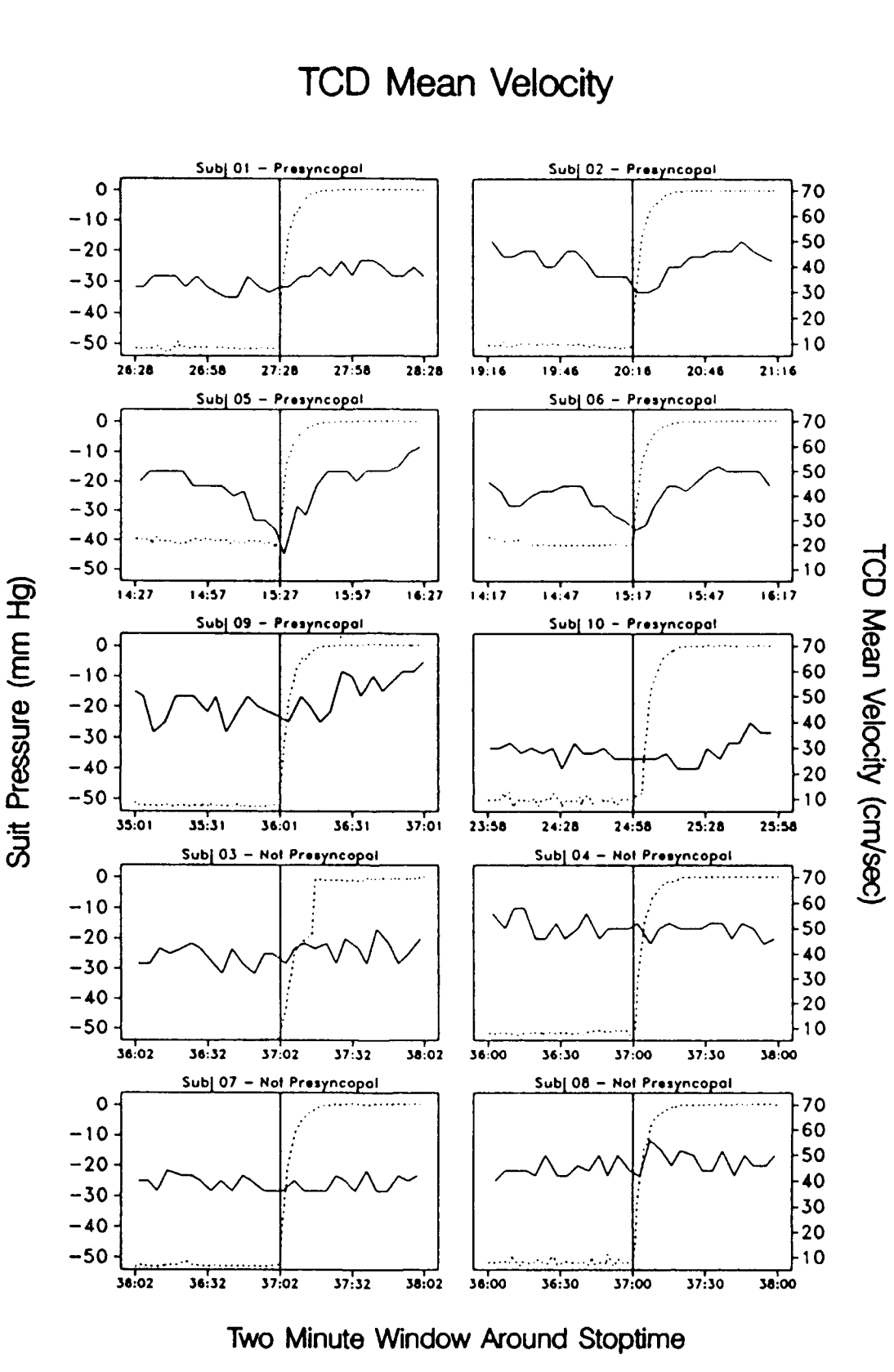

TCD Mean Velocity
Subj 01 – Presyncopal
Subj 02 – Presyncopal
Subj 05 – Presyncopal
Subj 06 – Presyncopal
Subj 09 – Presyncopal
Subj 10 – Presyncopal
Subj 03 – Not Presyncopal
Subj 04 – Not Presyncopal
Subj 07 – Not Presyncopal
Subj 08 – Not Presyncopal
Suit Pressure (mm Hg)
TCD Mean Velocity (cm/sec)
Two Minute Window Around Stoptime
Suit Pressure

FIGURE 9.

Pulsatility Index

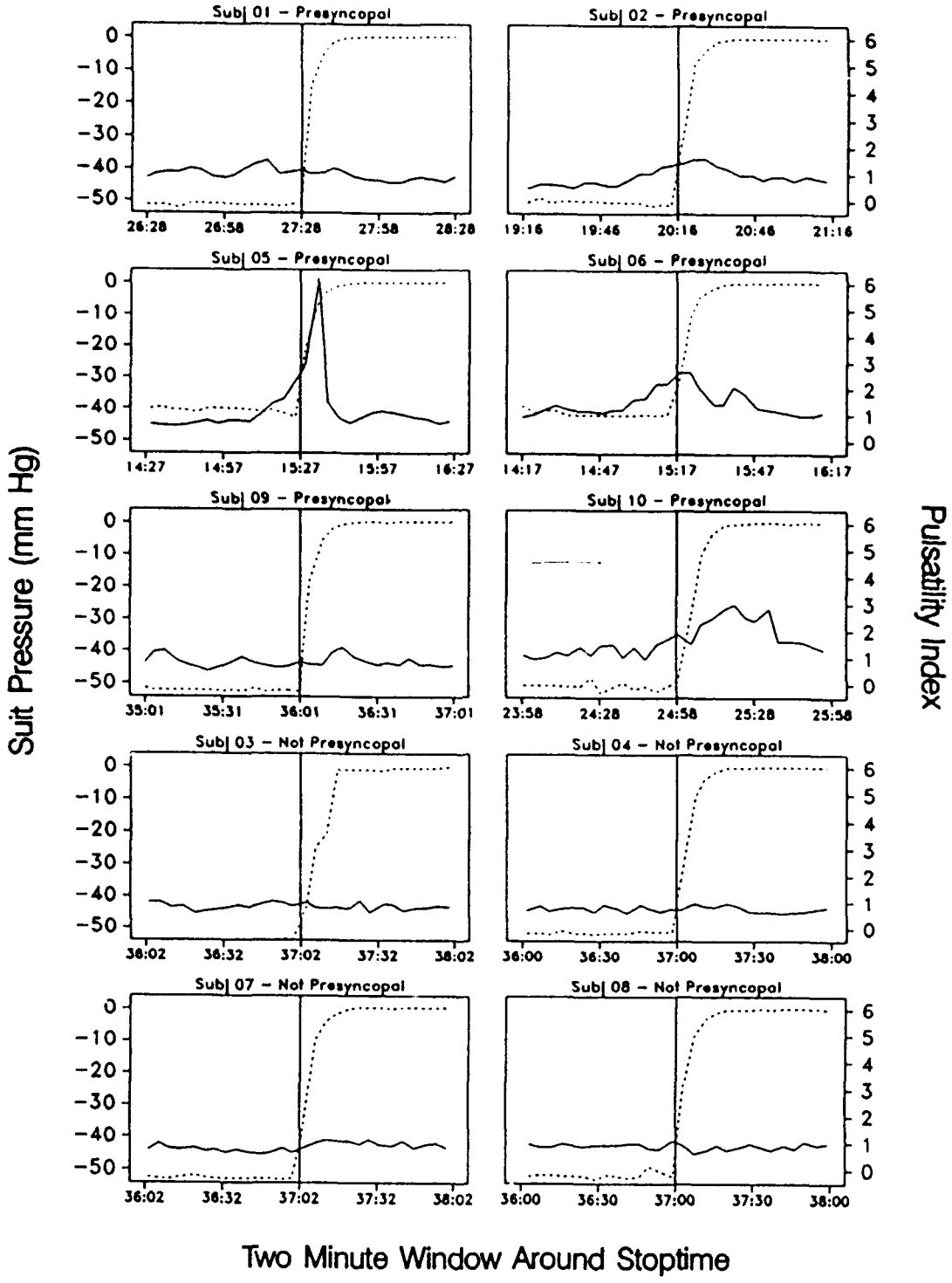
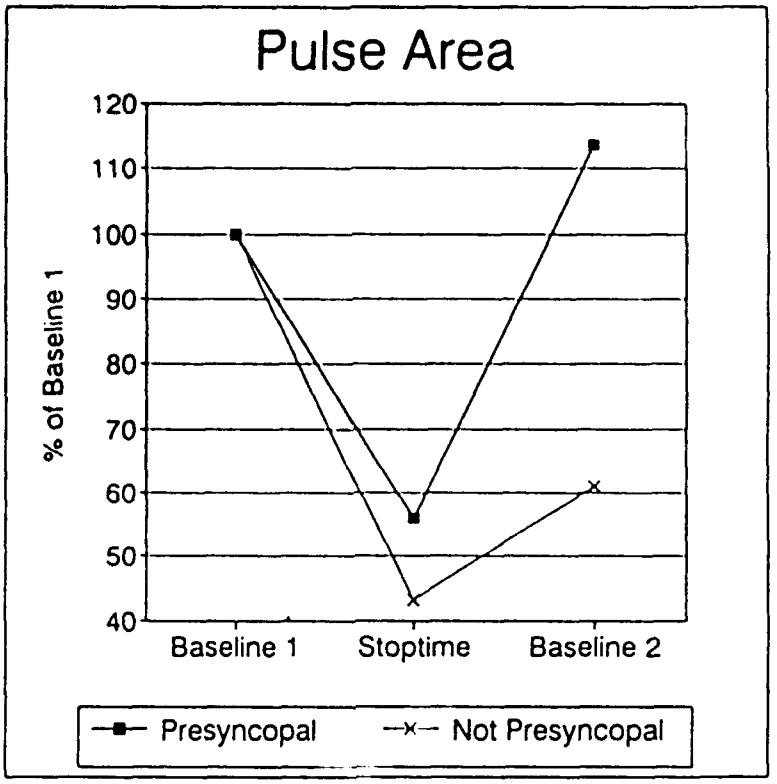


FIGURE 10.

Line And Bar Graph, Configured Internals.

Figures 11 through 16 illustrate the results for each of the six variables. All values are displayed as a percent of Baseline 1.

Each figure contains two graphs. The upper line graph shows the group mean at each experimental sampling point (Baseline 1, Stoptime, and Baseline 2). The lower graph shows the same values, with the whiskers extending from each bar representing the 95% confidence interval for the means.


Pulse Area
120
110
100
90
80
70
60
50
40
% of Baseline 1
Baseline 1
Stoptime
Baseline 2
Presyncopal
Not Presyncopal

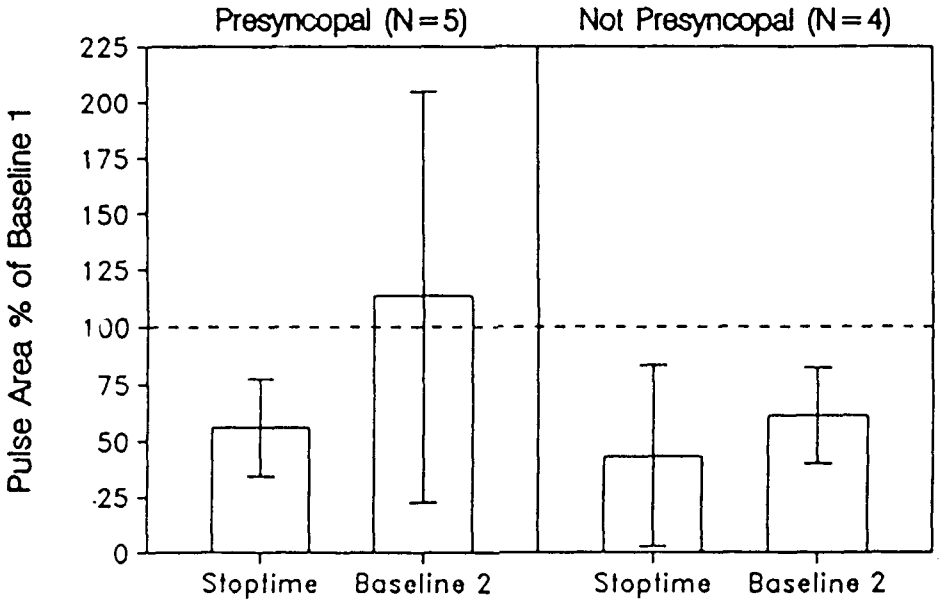
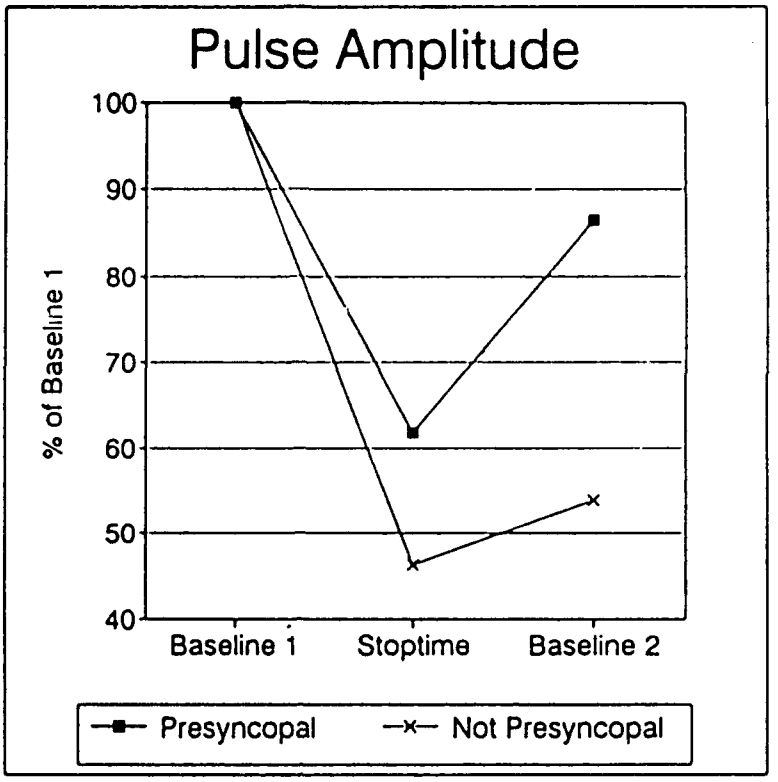

Presyncopal (N=5)
Not Presyncopal (N=4)
225
200
175
150
125
100
75
50
25
0
Pulse Area % of Baseline 1
Stoptime
Baseline 2
Stoptime
Baseline 2

FIGURE 11.


Pulse Amplitude
100
90
80
70
60
50
40
% of Baseline 1
Baseline 1
Stoptime
Baseline 2
Presyncopal
Not Presyncopal

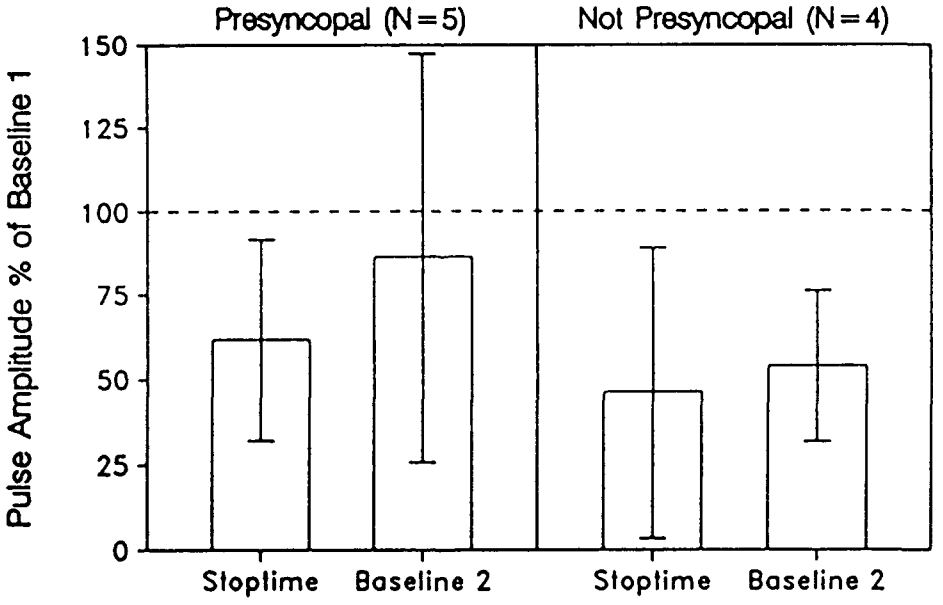
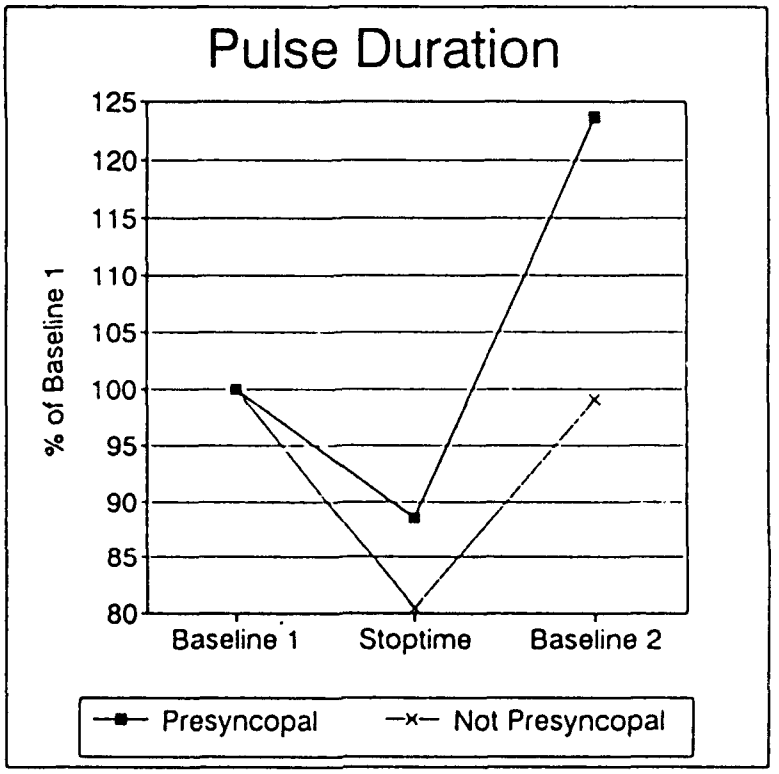

Presyncopal (N=5)
Not Presyncopal (N=4)
150
125
100
75
50
25
0
Pulse Amplitude % of Baseline 1
Stoptime
Baseline 2
Stoptime
Baseline 2

FIGURE 12.


Pulse Duration
% of Baseline 1
125
120
115
110
105
100
95
90
85
80
Baseline 1
Stoptime
Baseline 2
Presyncopal
Not Presyncopal

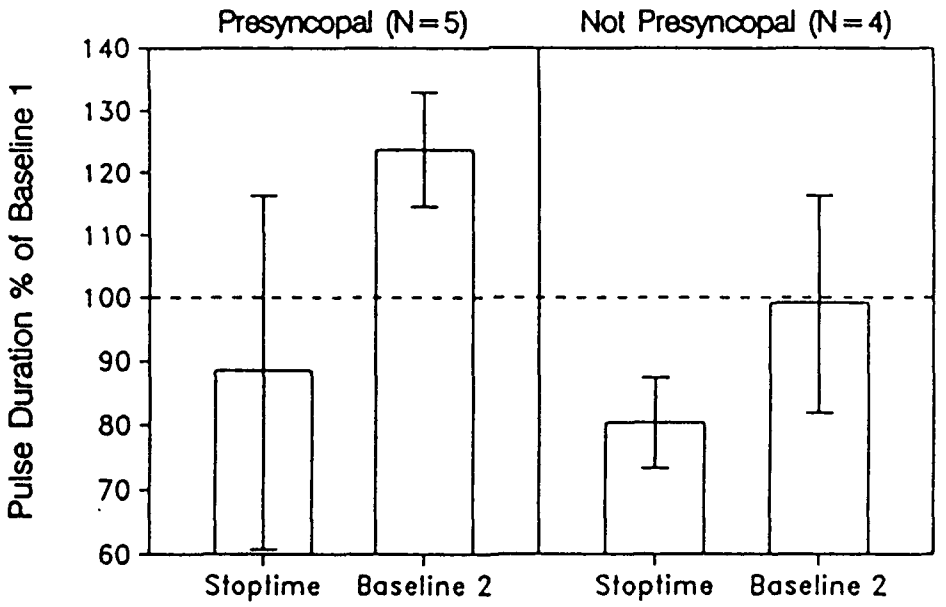
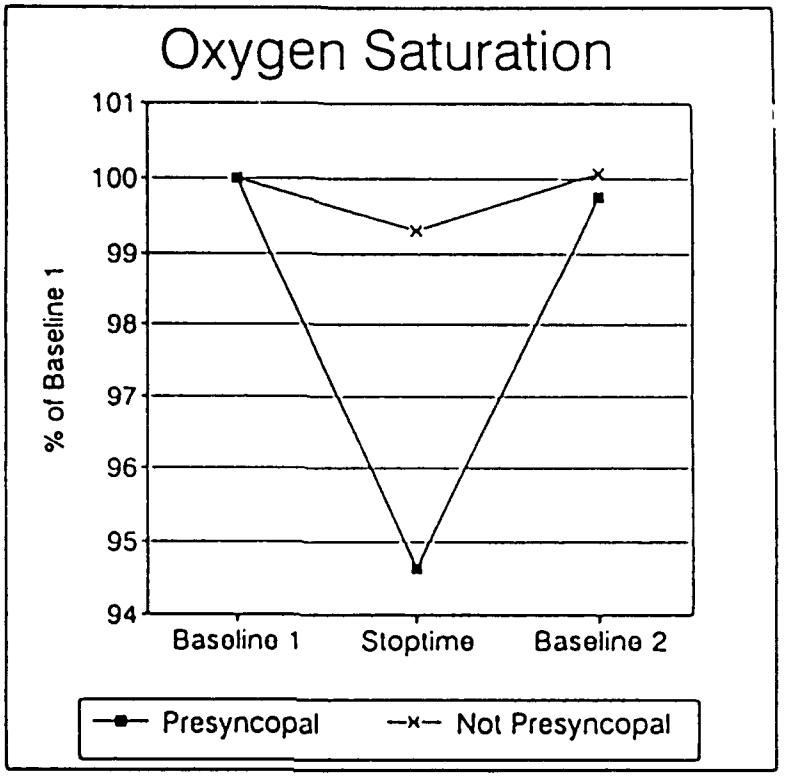

Presyncopal (N=5)
Not Presyncopal (N=4)
Pulse Duration % of Baseline 1
140
130
120
110
100
90
80
70
60
Stoptime
Baseline 2
Stoptime
Baseline 2

FIGURE 13.


Oxygen Saturation
101
100
99
98
97
96
95
94
% of Baseline 1
Baseline 1
Stoptime
Baseline 2
Presyncopal
Not Presyncopal

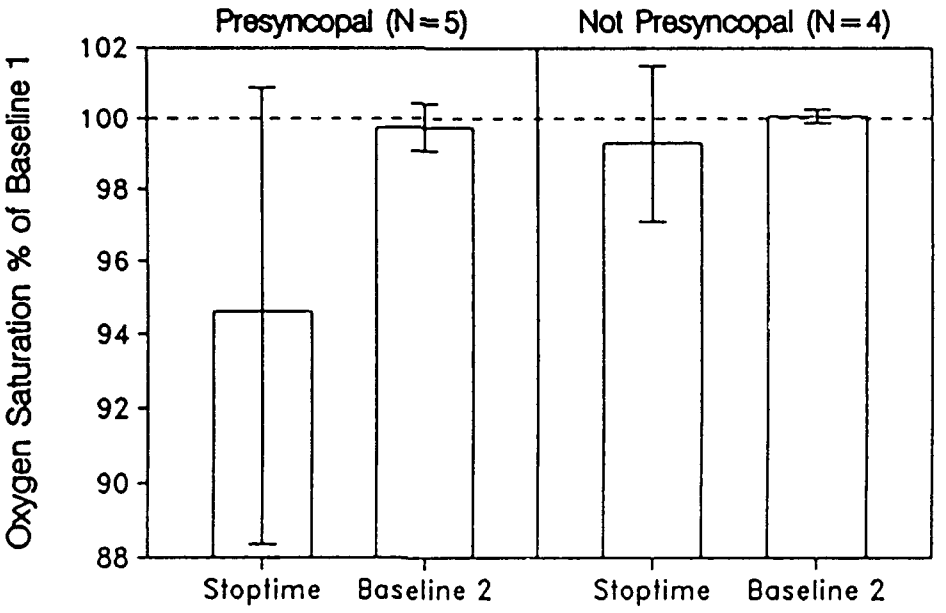
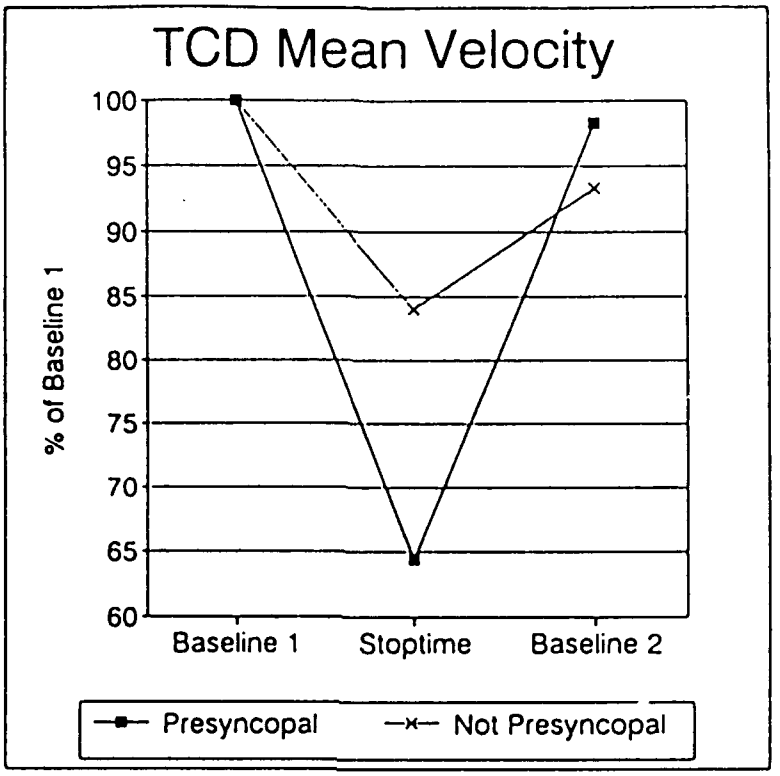

Presyncopal (N=5)
Not Presyncopal (N=4)
102
100
98
96
94
92
90
88
Oxygen Saturation % of Baseline 1
Stoptime
Baseline 2
Stoptime
Baseline 2

FIGURE 14.


TCD Mean Velocity
100
95
90
85
80
75
70
65
60
% of Baseline 1
Baseline 1
Stoptime
Baseline 2
Presyncopal
Not Presyncopal

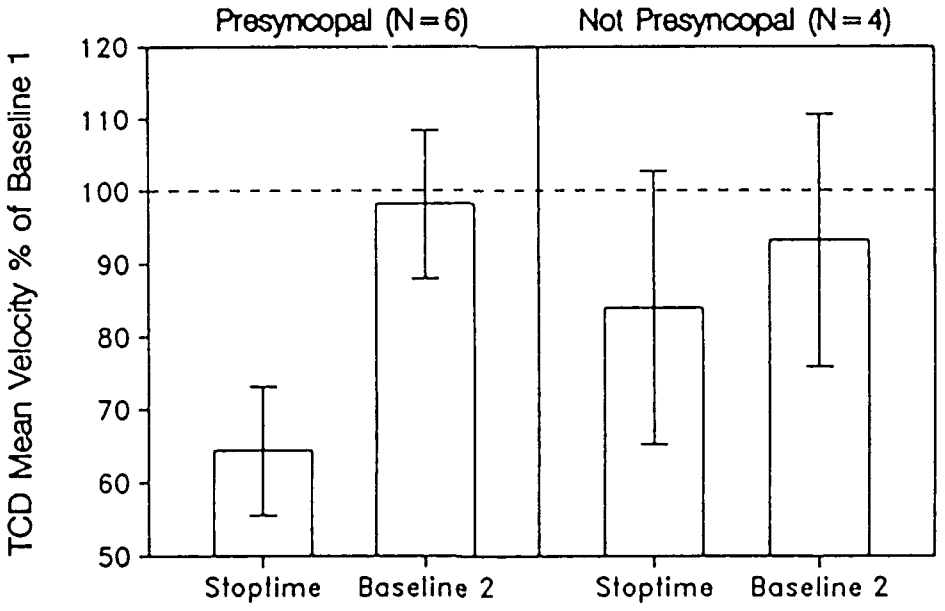
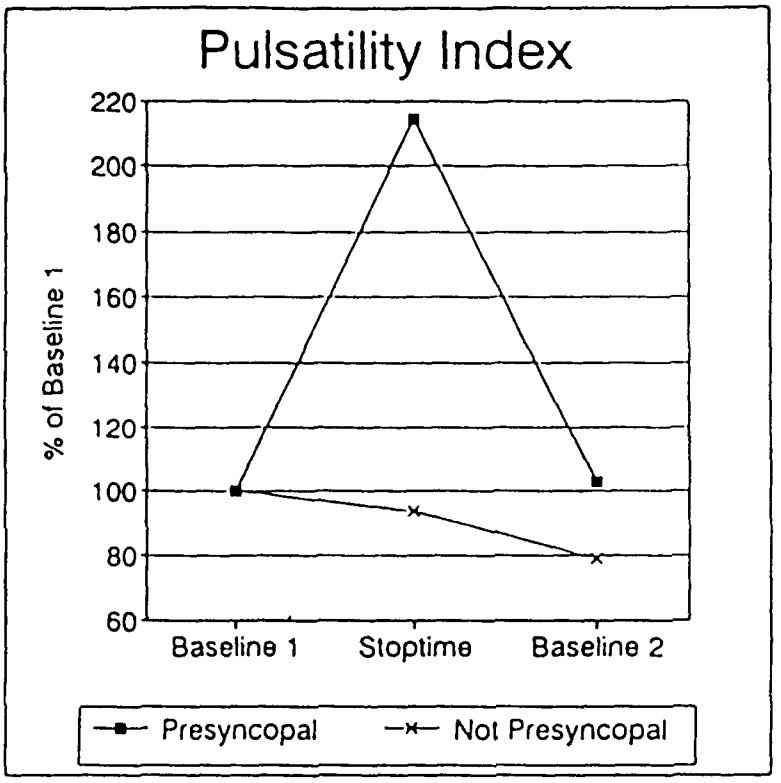

Presyncopal (N=6)
Not Presyncopal (N=4)
TCD Mean Velocity % of Baseline 1
120
110
100
90
80
70
60
50
Stoptime
Baseline 2
Stoptime
Baseline 2

FIGURE 15.


Pulsatility Index
220
200
180
160
140
120
100
80
60
% of Baseline 1
Baseline 1
Stoptime
Baseline 2
Presyncopal
Not Presyncopal

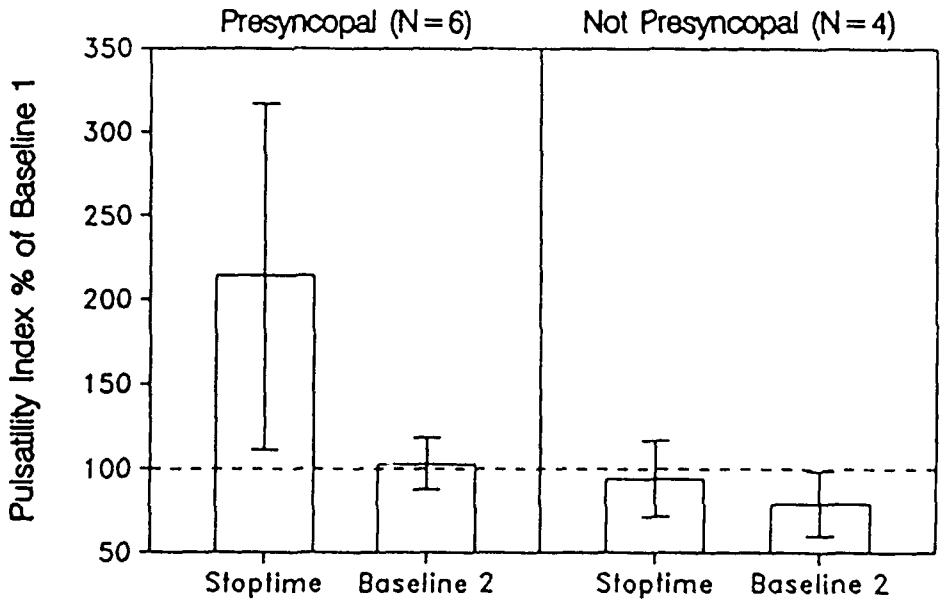

Presyncopal (N=6)
Not Presyncopal (N=4)
350
300
250
200
150
100
50
Pulsatility Index % of Baseline 1
Stoptime
Baseline 2
Stoptime
Baseline 2

FIGURE 16.

Graphs: Percent Of Baseline 1

The following plots in Figure 17 show each variable, displayed as a percent of Baseline 1, at STOPTIME (experimental endpoint) and Baseline 2. Both groups are simultaneously displayed. Baseline 1 represents 100%. In addition, the y-axis scale is identical in all graphs.

N = 4 for all variables involving the non-presyncopal group.

N = 5 for the presyncopal group variables AREA, AMPLITUDE, DURATION, and OXYGEN SATURATION.

N = 6 for the presyncopal group variables TCD MEAN VELOCITY and PULSATILITY INDEX.

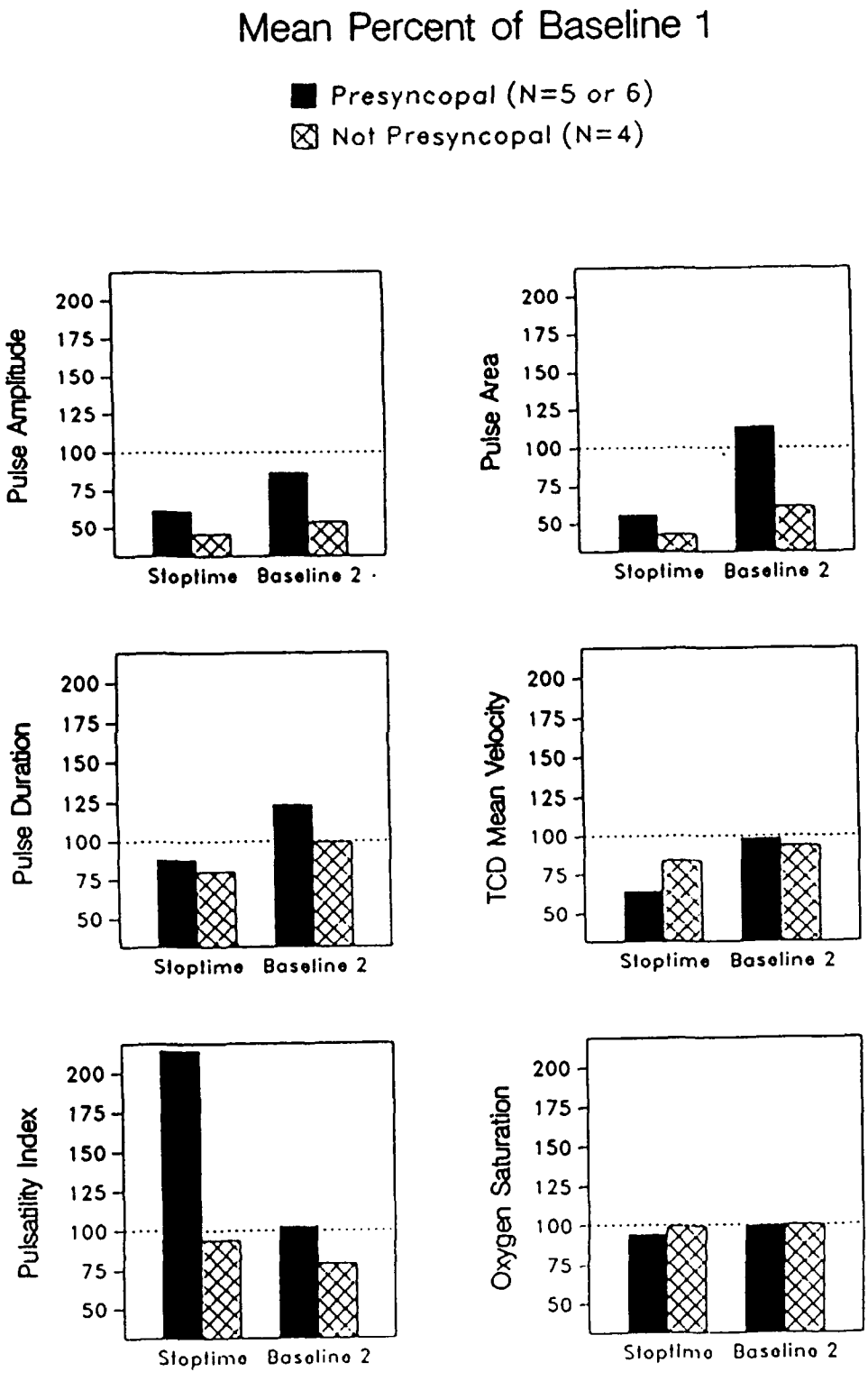

Mean Percent of Baseline 1
Presyncopal (N=5 or 6)
Not Presyncopal (N=4)
Pulse Amplitude
Pulse Area
Pulse Duration
TCD Mean Velocity
Pulsatility Index
Oxygen Saturation
200
175
150
125
100
75
50
Stoptime
Baseline 2

FIGURE 17.

DISCUSSION

Pulse Waveform During LBNP

Changes in the pulse oximeter waveform signal have several potential causes. Ultimately, they include any changes which modify the amount of infrared and red light absorbed as detected by the sensor [40, 41, 42, 45]. Since the amount of tissue and bone remains constant, the amount of light absorbed by blood is the variable. Potential factors which could alter this analog signal waveform include sensor clip positional change, ear tissue compression by the sensor clip, changes in oxygen saturation (% SaO2), peripheral vasoconstriction, intravascular blood volume changes, and motion artifact. Sensor clip positional change was not felt to play a significant role because the subjects remained in a stationary position. Multiple repeated test measurements during the design of this experiment for significant periods of time at ambient pressure did not demonstrate the same changes that occurred during LBNP, making tissue compression an unlikely influence. In addition, the fact that the pulse waveform signal amplitude consistently increased after discontinuation of LBNP indicated the change was because of blood flow, not artifact. Since the sensor measures spectrophotometric absorption, a change in the oxygen saturation of the blood could also change the shape of the pulsatile signal. In this experiment, the pulse waveform area and amplitude generally changed prior to the time that oxygen saturation decreased.

Pulse Waveform Area During LBNP

The analog pulse waveform area exhibited relative stability during the baseline portion of the LBNP profile. Upon exposure of the subject to negative pressure, the pulse waveform area began to gradually decrease, consistent with pooling of blood in the lower one-half of the body and a decreased central blood volume. After discontinuation of negative pressure, it increased toward the original steady state baseline. In several subjects, it exhibited an "overshoot", analogous to a "reactive hyperemic" response of the peripheral or cerebral circulation [4,12].

The pulse waveform area decreased below the initial baseline in both the presyncopal and non-presyncopal groups. Overall, the percentage decrease was greater in the non-presyncopal group (56.86% mean percent decrease vs. 43.99% in the presyncopal group). However, this small difference must be cautiously interpreted because of the small number of subjects in each group. It may also reflect differences in LBNP tolerance.

It is important to realize that both of the groups were exposed

to the same negative pressure profile and therefore experienced the physiological effects of LBNP. This explains why pulse waveform area decreased significantly in both groups.

The decrease in pulse area during LBNP is consistent with the physiological pooling of blood in the lower one-half of the body, away from the upper body and head where the sensor was located.

The pulse waveform area decrease was not a smooth gradual curve. Motion artifact was easily identifiable by sudden, extremely large changes in pulse area which ceased upon discontinuation of movement. In addition, while the overall trend was a continual decrease, small increases followed by decreases were also continuously apparent in the data. These data are illustrated in Appendix L. The observed effect may be partly related to a phenomenon observed by Buick et al., using ear opacity techniques during exposure to gradual onset +Gz [34]. They observed cyclical changes in the ear opacity pulse with a mean cycling period of 10.4 seconds [34]. The mean difference in opacity level within cycles was 17.1% of the +1 Gz opacity value [34]. Their results suggested that head-level perfusion may not be constant during sustained +Gz [34].

Pulse Waveform Amplitude During LBNP

The pulse waveform amplitude demonstrated changes similar to pulse waveform area. After a stable baseline, the amplitude began to gradually decrease upon application of LBNP. Upon discontinuation of the pressure, this amplitude again returned toward the original baseline value.

The pulse waveform amplitude likewise demonstrated a significant decrease relative to the initial baseline in both the presyncopal and non-presyncopal groups. Overall, the percentage decrease was greater in the non-presyncopal group (53.75 mean percent decrease vs. 38.27% decrease in the presyncopal group). This might be explained by a difference in tolerance to LBNP between the groups. It is important to remember that both groups were exposed to LBNP and therefore experienced the pooling of blood associated with LBNP.

The decrease in pulse amplitude during LBNP is consistent with the physiological pooling of blood in the lower one-half of the body, away from the upper body and head where the sensor was located.

Pulse Duration During LBNP

As previously discussed and described in Figure 7, the pulse duration represents the time interval (measured in milliseconds) from the beginning to the end of a particular pulse waveform. Pulse duration is inversely related to heart rate. Faster heart rates result in a greater number of pulse waveforms per unit time, therefore the pulse duration is smaller. Slower heart rates will have a longer pulse duration value.

Overall, both groups demonstrated a decrease in pulse duration at the experimental endpoint, consistent with an increase in heart rate. The actual percent change from baseline was only significant in the non-presyncopal group. Upon examination of the values for each individual subject, all non-presyncopal subjects and 4 of the 5 presyncopal subjects (for whom duration values were analyzed) demonstrated a decrease in pulse duration. This is consistent with an increase in heart rate prior to the endpoint. Because of the small group size (N = 5) in the presyncopal group, the effect of one subject's (subject 05) increase in pulse duration (decrease in heart rate) at the endpoint effectively cancelled out the statistical significance of the other 4 subjects in that group.

The increase in heart rate in all but one subject is consistent physiologically with the increased workload experienced by all subjects during this exposure to LBNP. In addition, it may also be partly explained by a tachycardic response to decreased central blood volume. The one subject (subject 05) who actually demonstrated a decrease in heart rate at the endpoint may have been experiencing a bradycardic or vasovagal response with impending cardiovascular decompensation. This subject, in fact, did experience the most significant presyncopal symptoms of the entire group. This subject also demonstrated the largest changes in TCD mean velocity, pulsatility index, and oxygen saturation.

Oxygen Saturation During LBNP

Oxygen saturation, as measured by the pulse oximeter, tended to remain very stable until just prior to the presyncopal endpoint. In several of the presyncopal subjects, it rapidly decreased shortly before the endpoint. Upon discontinuation of negative pressure and restoration of central volume and cerebral blood flow, it again quickly returned to baseline values.

The observed changes at STOPTIME relative to Baseline 1 were not statistically significant in either group. This, however, is explained by the fact that oxygen saturation did not decrease in all of the presyncopal subjects. Considerable changes in oxygen saturation were observed in three of the presyncopal subjects at STOPTIME. In those subjects, oxygen saturation decreased by 11%,

10%, and 4.9% of the Baseline 1 value. Two of the presyncopal subjects did not demonstrate any meaningful changes in oxygen saturation at the endpoint. As a result, the statistical result for the presyncopal group as a whole was not significant. In the non-presyncopal group, there were essentially no changes in oxygen saturation for any subject.

Transcranial Doppler During LBNP

The cerebral circulation generally demonstrates a high degree of autoregulation between arterial pressures of 60 to 160 mm Hg [4]. Pressures below 60 mm Hg result in reduced cerebral blood flow and syncope [4]. The exact etiology of this auto-regulation is unknown, but evidence favors a metabolic source [4]. Cerebrovascular auto-regulation occurs at the arteriolar level [12]. The cerebral arterioles normally dilate in response to decreases in blood pressure and constrict with increased blood pressure [12]. The net effect is to maintain a constant flow. In general, hypoxia causes cerebral vasodilatation and increased cerebral blood flow [18, 33].

Gosling's pulsatility index (P.I.), as utilized in transcranial ultrasonography, is an indicator of vascular resistance. The Pulsatility Index increases with arteriolar vasoconstriction/vasospasm distal to the insonation point and decreases with arteriolar vasodilation [12, 19].

Transcranial Doppler sonography is generally regarded as an accurate method of determining blood flow velocity and changes in cerebral vascular resistance, provided that the diameter of the middle cerebral artery (MCA) remains constant [12]. Several studies have demonstrated that changes in the diameter of the MCA are very small, being in the range of 10 to 15% [12]. This is essentially insignificant when compared to the changes in diameter which can occur in cerebral arterioles [12].

The TCD results during the LBNP exposures in this experiment demonstrated little or no change in mean cerebral blood flow and pulsatility index until shortly before the presyncopal endpoint. This can most likely be explained by the presence of cerebral auto-regulation [4], which would attempt to maintain blood flow to the brain fairly constant until cardiovascular decompensation began to occur.

Shortly before the presyncopal endpoint, mean cerebral blood flow velocity decreased sharply. Simultaneously, pulsatility index tended to quickly increase. Upon discontinuation of the LBNP influence, blood flow to the head was restored and these values soon returned toward their baseline values. Often, there was an overshoot in cerebral blood flow velocity for a brief period of

time past the original baseline values, possibly attributable to reactive hyperemia which can occur in the cerebral circulation [4,12].

In the non-presyncopal group, TCD mean velocity decreased to 84.0% of its Baseline 1 value at the experimental endpoint. Pulsatility index decreased to 94.1% of its Baseline 1 value at the endpoint. Both of these changes were not statistically significant in the non-presyncopal group. There was, however, a definite decreasing trend of TCD mean velocity.

In the presyncopal group, TCD mean velocity decreased to 64.4% of its baseline 1 value at the experimental endpoint. Pulsatility index increased to 214.2% of its baseline 1 value at the endpoint. Both of these changes were statistically significant in the presyncopal group.

The pulsatility index (P.I.) demonstrated some of the most dramatic changes of any of the variables measured just prior to the presyncopal endpoint. Individual subject P.I. values ranged from 127.4% to 403.6% of Baseline 1 (mean 214.235%, s.d. 98.1039%) in the presyncopal group, and only 79.4% to 112.4% of Baseline 1 (mean 94.115%, s.d. 14.1586%) in the non-presyncopal group.

The results obtained suggest that paradoxic cerebral vasoconstriction occurred just prior to and during the presyncopal endpoint, similar to the results obtained by Grubb et al., during head-upright tilt-table induced vasovagal syncope [12].

Work performed by Ueno et al., studying the effect of LBNP on the cerebral circulation suggests that exposure to moderate (non-presyncopal) LBNP causes a decrease in cerebral blood flow with a compensatory cerebrovascular vasodilation [46].

The results obtained in this experiment suggest that alterations in cerebral autoregulation may occur just prior to the presyncopal endpoint during LBNP, consistent with the findings of Grubb et al., during tilt-table induced syncope [12].

Recent human centrifuge work by Ossard et al., has indicated that mean cerebral blood flow velocity is significantly decreased during G-onset and also during plateaus from +2 to +4 Gz [44].

Return To Baseline Values

The six variables previously discussed were also analyzed as to whether or not they returned toward the Baseline 1 value after discontinuation of LBNP. This was performed by comparing the percent change from Baseline 1 to Baseline 2 using a Student's t-test, with an alpha value of 0.05.

In the non-presyncopal group, TCD mean velocity, Pulsatility Index, Oxygen Saturation, and Pulse Duration demonstrated no significant difference between Baseline 1 and Baseline 2.

In the non-presyncopal group, Pulse Area and Pulse Amplitude all demonstrated a trend toward the original baseline. It should be emphasized that a definite trend was apparent, and that these variables were measured only five minutes after discontinuation of LBNP. It is presumed that had these variables been measured again in five or ten minutes, they would have shown a continuing trend and perhaps a complete return to their original baseline values. In addition, the non-presyncopal subjects remained standing during the five minutes of Baseline 2 whereas the presyncopal subjects assumed a seated position. This most likely influenced blood and interstitial fluid return, slowing the recovery to baseline after LBNP.

In the presyncopal group, all variables except for pulse duration demonstrated a return to baseline. Pulse duration was longer at Baseline 2 than at Baseline 1 in the presyncopal group, indicating that heart rate was slower. This was statistically significant with a p-value of 0.0020. Duration is inversely related to heart rate. A faster heart rate will cause a larger number of pulses per unit time, and consequently a smaller time interval per pulse. At the experimental endpoint, pulse duration actually decreased below its Baseline 1 value indicating an increase in heart rate. After discontinuation of pressure, the pulse duration again increased toward the Baseline 1 value and actually surpassed the original value. In other words, the group mean heart rate was lower at Baseline 2 than at Baseline 1.

Differences Between Groups At Stoptime

As previously discussed, a two-sample t-test was performed to detect a difference between the presyncopal and non-presyncopal groups at the experimental endpoint (STOPTIME). The resulting P-values were previously listed in Table 6. At an alpha level of 0.05, only TCD mean Velocity and Pulsatility Index demonstrated a statistically significant difference at STOPTIME between groups. The variables pulse area, pulse amplitude, pulse duration, and oxygen saturation did not demonstrate a statistically significant difference between groups at the endpoint. It must again be emphasized that both groups experienced the physiological effects and pooling of blood caused by LBNP. Although the results for oxygen saturation were not statistically different between groups, the mean SaO_2 value for the presyncopal group was 4.69% lower than the non-presyncopal group. In addition, three of the six presyncopal subjects demonstrated considerable decreases in SaO_2 at STOPTIME.

(Subject 05 showed an 11% decrease in SaO_2, subject 01 showed a 10% decrease in SaO_2, and subject 10 showed a 4.9% decrease in SaO_2 at STOPTIME). A similar phenomenon did not occur in the non-presyncopal group.

These results suggest that TCD mean velocity and pulsatility index were the most effective in actually detecting the presyncopal endpoint during LBNP exposure since these were the only two variables that showed a statistically significant difference between groups at the endpoint.

Warning Interval

Changes in several of the variables measured provided a "warning interval" just prior to subject abort/presyncope. The "warning interval" was defined as "the onset of a significant trend in a physiological variable, occurring prior to the presyncopal endpoint, which continued until the endpoint was reached, and reversed itself upon discontinuation of LBNP."

The warning interval was most apparent in TCD mean cerebral blood flow velocity, pulsatility index, and oxygen saturation. In contrast, the pulse waveform tended to gradually decrease in area and amplitude upon application of negative pressure, with a minimal value at the point of presyncope. The pulse waveform subsequently returned toward baseline after discontinuation of the negative pressure. This effect is presumably related to the gradual pooling of blood in the lower one-half of the body. Peripheral vasoconstriction may have also played a role in this phenomenon. Since the pulse waveform sensor site was the ear lobe, it did not directly measure deep cerebral blood flow.

Oxygen saturation levels tended to remain stable until shortly before presyncope, when they decreased by 11%, 10%, and 4.9%, respectively, in three of the subjects. SaO_2 did not decrease in all presyncopal subjects, possibly attributable to the subjective nature of the experimental endpoint and differences in tolerance to LBNP. The SaO_2 began to decrease between 12-21 seconds before the presyncopal endpoint in three of the subjects. The SaO_2 subsequently returned to baseline after discontinuation of pressure, presumably due to restoration of central blood volume.

The transcranial Doppler mean velocity signal demonstrated impressive decreases in cerebral blood flow velocity prior to the presyncopal endpoint. In addition, the pulsatility index tended to increase above a value of 1.0 for a significant period of time prior to the experimental endpoint. This time period was often 20 seconds or longer.

TABLE 6. APPROXIMATE WARNING INTERVAL PRIOR TO STOPTIME
TCD Mean

SUBJECT	SaO_2	P.I.	Velocity
01	21 sec	22 sec	30 sec
02	NONE	15 sec	15 sec
05	12 sec	15 sec	11 sec
06	N/A	51 sec	17 sec
09	NONE	NONE	09 sec
10	20 sec	50 sec	80 sec

Note: Times listed are in seconds prior to STOPTIME.
All subjects above experienced presyncopal symptoms and were unaware of any changes seen on the monitoring devices.

Although Table 6 was subjectively determined by visually examining the data trends, it effectively illustrates the "warning interval" for several variables of the presyncopal group. Trends for pulse waveform area and amplitude began with the onset of LBNP, and reversed upon discontinuation of negative pressure. Actual warning trend data are shown in Appendix N.

Subjective Nature Of Presyncopal Symptoms

Since the stop point was under subject control, the endpoints all varied depending upon the individual symptom tolerance of each subject. In other words, some subjects may have aborted sooner than others in relation to severity of symptoms. This most likely explains why certain variables (such as SaO_2) did not change significantly in all subjects experiencing "presyncopal" symptoms.

Comments And Limitations

Because of unavoidable limitations, only ten subjects were able to be included in this study. Furthermore, only six of the ten actually reached the desired endpoint. Obviously, a larger number of subjects would be desirable for any type of statistical analysis and conclusion. The small number of subjects in each group had great impact on the ability to demonstrate statistical significance in several variables.

This study was performed in a 1 G static environment. In order to validate this method of real-time analysis, a similar study should be performed analyzing the pulse waveform during exposure to +Gz.

In this experiment, all of the subjects did not reach the presyncopal endpoint. This was due to limitations of the amount of negative pressure available from the vacuum source. Ideally, a continuous pressure ramp until onset of symptoms could have been used which would have increased the number of presyncopal subjects.

In most LBNP research, the subject is in a supine or seated position. This experiment required the additional gravity gradient available in the standing position because of limitations in the vacuum source.

The site chosen for the pulse oximeter sensor was the earlobe. The arterial blood supply to the ear lobe is derived from the posterior auricular artery (a branch of the external carotid), the anterior auricular artery (a branch of the superficial temporal artery), and an arterial branch from the occipital artery [11]. Ultimately, these all arise from the external carotid artery [11]. Several other locations were evaluated, including the use of reflectance transducers which can be placed virtually anywhere on an exposed skin surface. The nasal septum, whose blood supply is derived from the internal carotid artery through branches of the enthmoid artery [11], was considered as a possible site, but we were unable to obtain a reliable sensor configuration at this location.

In several cases, the return to baseline would have been more complete if several of the variables had been measured longer than five minutes after the experimental endpoint.

In the non-presyncopal group, the return of several variables to baseline would have been improved by having the subject assume a seated position. The presyncopal group was placed in a seated position after reaching the endpoint. This difference most likely explains the delayed return to baseline of pulse area and amplitude in the non-presyncopal group.

As previously mentioned, the pulse oximeter sensor used was extremely sensitive to motion artifact. Stabilization of the head and sensor unit would have decreased this effect. Pulse oximeters are available which utilize the R-wave of the ECG to automatically synchronize the identification of the beginning of a new pulse [45]. A similar method could be used to improve the tracking and analysis of pulse waveforms and eliminate much artifactual data.

Blood pressure and heart rate were continuously monitored throughout the experiment. These were mainly for medical monitoring purposes, and were not included in the final analysis

as the responses of heart rate and blood pressure to LBNP are already well-studied. Had analysis of heart rate and blood pressure been attempted, it would have been complicated by large gaps of missing data which occurred during re-calibration of the blood pressure unit that was utilized.

System For Detecting Presyncope/GLOC

Based on the results of this experiment, it would seem that the best arrangement for a system to detect presyncope/GLOC would be a combination of physiological sensors, without relying on a single system. For example, oxygen saturation decreased sharply in some but not all subjects. Similarly, there were varying degrees of change between subjects in cerebral blood flow velocity prior to presyncope.

Physiological variables including heart rate, oxygen saturation, pulse oximeter analog waveform, TCD cerebral blood flow velocity, and TCD pulsatility index all have potential applicability in such a system.

If the pulse oximeter was to be used in a warning or feedback device, a stable platform would be required for the sensor to reduce the motion artifact inherent in an operational environment.

The possibility of building many of these sensors into a crewmember's helmet and/or life support equipment is technically quite feasible and has already been accomplished, for the most part, at Wright-Patterson Air Force Base [24].

CONCLUSIONS

This study evaluated a method for measuring and quantifying changes in the pulse waveform analog signal during LBNP. This information was collected and simultaneously compared with other physiological variables including arterial oxygen saturation and cerebral blood flow. The intent was to simulate exposure to +Gz, and to determine if changes in any of these variables could be used to detect or predict presyncope.

Statistically significant changes in physiological variables were detected prior to termination of pressure during presyncopal LBNP.

These changes included:

1) Decreased pulse waveform area
2) Decreased pulse waveform amplitude
3) Decreased mean cerebral blood flow velocity
4) Increased cerebral blood flow pulsatility index

In addition, considerable changes in oxygen saturation were observed in several individual presyncopal subjects.

A significant "warning interval" was seen prior to presyncope, including large changes in oxygen saturation, mean cerebral blood flow velocity, and pulsatility index just prior to the experimental endpoint. The pulse waveform area and amplitude, although showing significant decreases consistent with blood pooling due to exposure to LBNP, did not display any sudden changes just prior to presyncope. Instead, pulse area and amplitude decreased in a gradual trend which began with the onset of LBNP, and reversed upon discontinuation of the negative pressure.

TCD mean velocity and Pulsatility index were the most effective in detecting a difference between the presyncopal and non-presyncopal groups at the experimental endpoint.

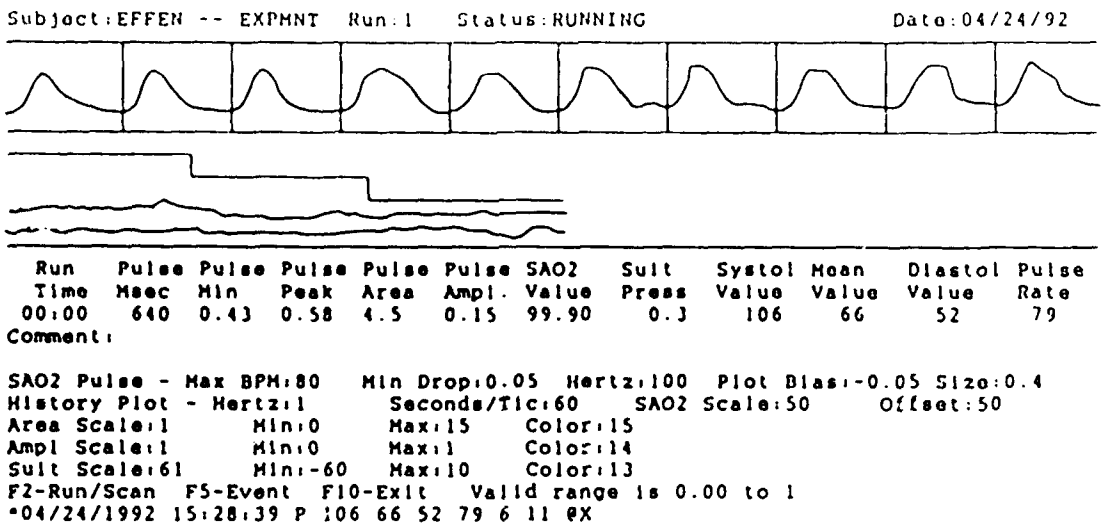
The results obtained suggest the possibility of using several of these devices in conjunction to detect impending syncope. Since LBNP is an analog of +Gz [13, 20], detection and warning of impending GLOC could also be possible.

Potential applications of these methods include monitoring and early detection of presyncope/GLOC during Space Shuttle operations including landing/re-entry, Space Station Assured Crew Return Vehicle re-entry, the National Aerospace Plane, +Gz exposure, and ground based or orbital LBNP experiments. This information could be used for remote medical monitoring or as physiological feedback to a pilot, crewmember, or safety control system [10, 28, 29, 30, 31].

APPENDICES

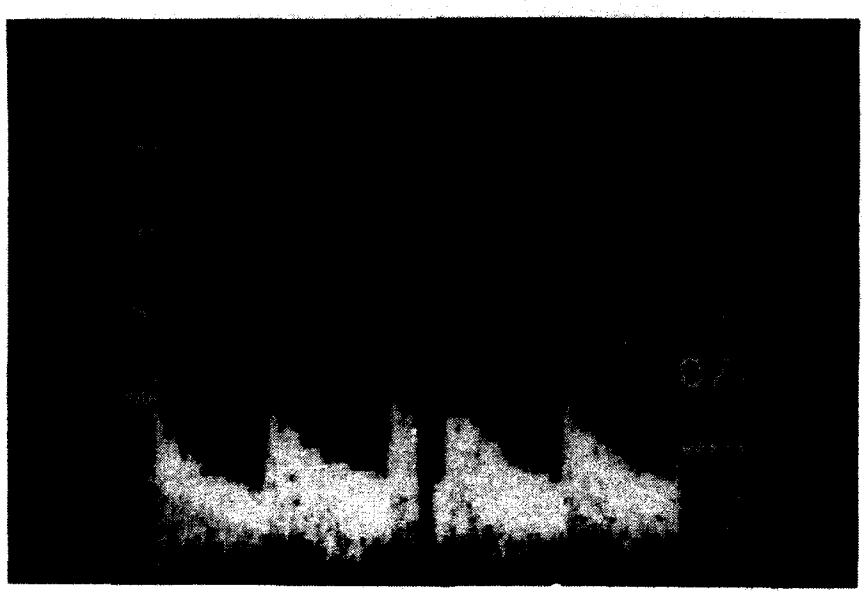
APPENDIX A. COMPUTER PROGRAM SCREEN DISPLAY

The following figure is an example of the computer screen display which was available throughout the experiment:



APPENDIX B. TRANSCRANIAL DOPPLER PROBE AND SCREEN DISPLAY

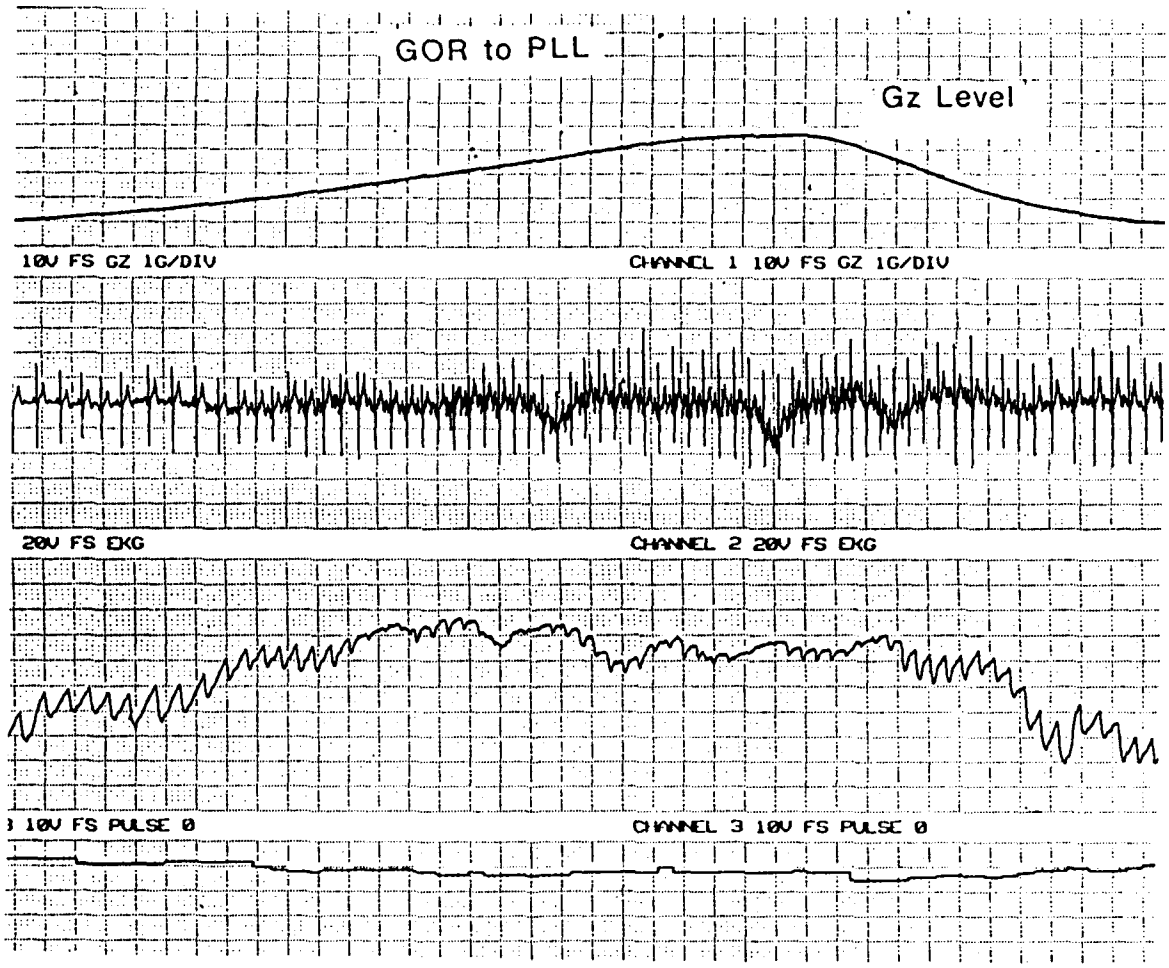
The photographs in this appendix show the TCD probe/head mount assembly, followed by an example of the TCD screen which was continuously displayed during the experiment:



APPENDIX C. PULSE WAVEFORM CHANGE DURING $+G_Z$

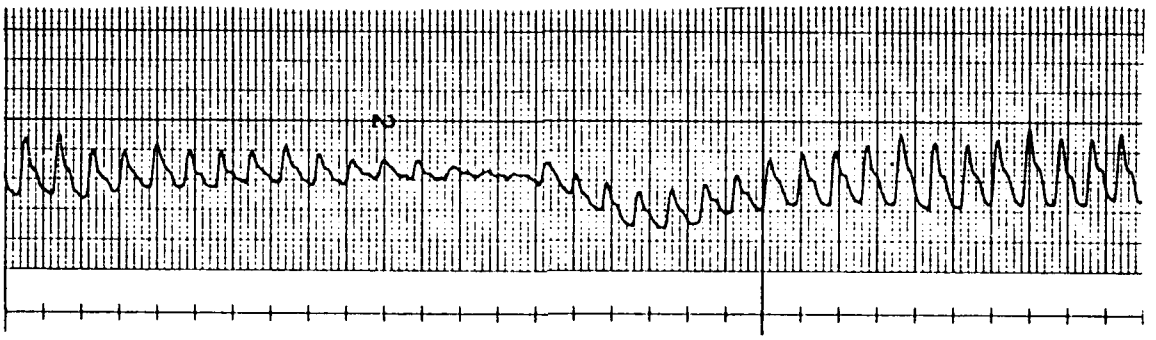
The following figure demonstrates an example of pulse waveform changes during $+G_Z$ on the human centrifuge (DES) at Wright-Patterson Air Force Base:

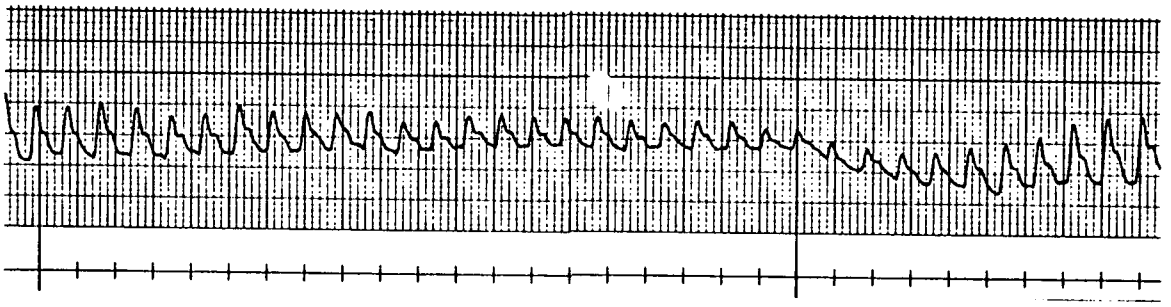
Note:
GOR to PLL = Gradual onset run to peripheral light loss.
Top graph represents $+G_Z$ value
2nd graph represents ECG waveform
3rd graph represents pulse oximeter waveform
4th graph represents oxygen saturation



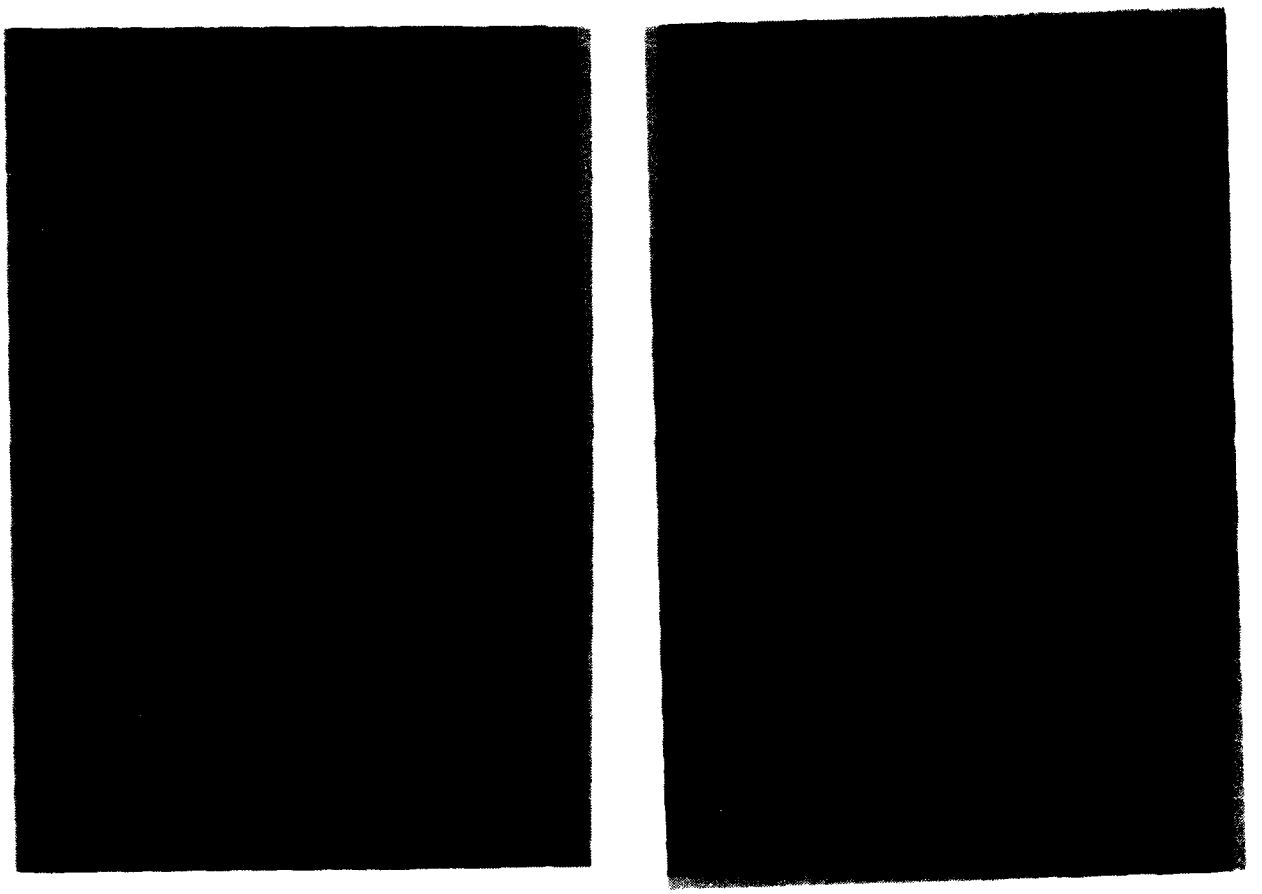
APPENDIX D. EFFECT OF ARTERIAL OCCLUSION ON PULSE WAVEFORM

The following strip charts demonstrate the effect of occluding the brachial artery with a blood pressure cuff on a fingertip pulse oximeter waveform.

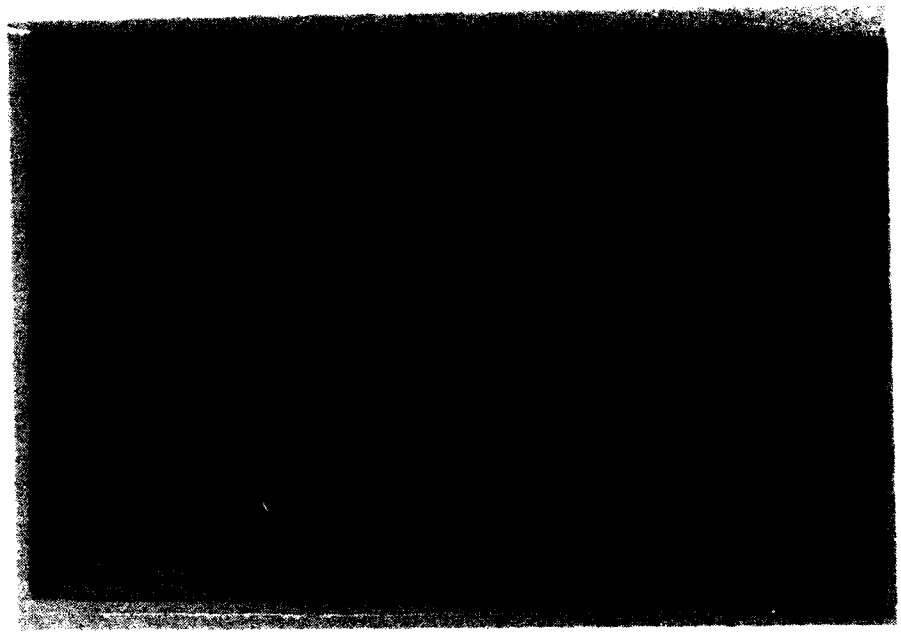


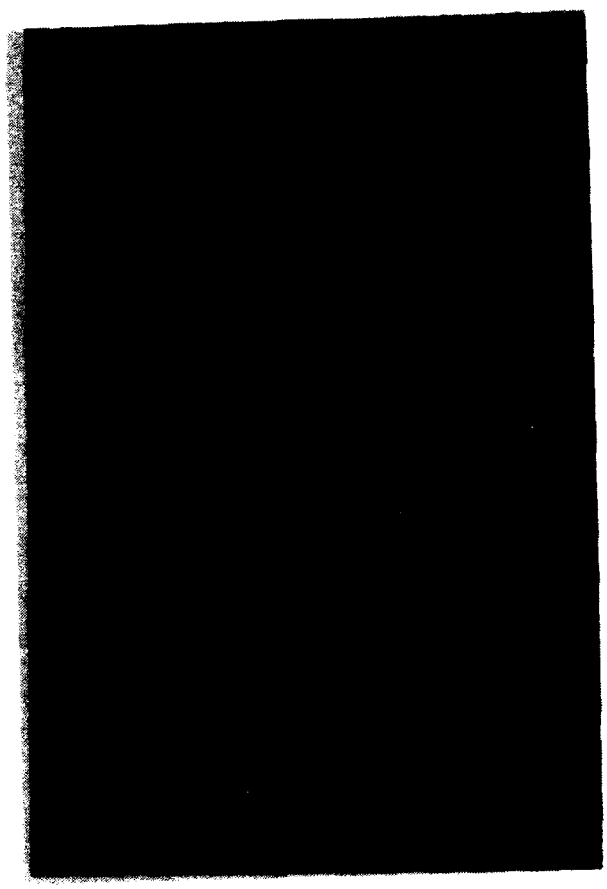


APPENDIX E. SUBJECT WEARING LBNP SUIT



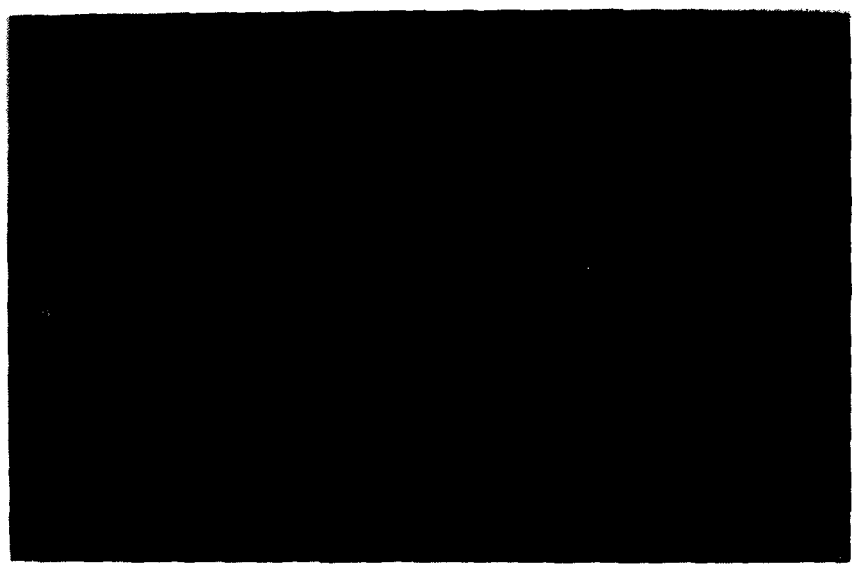
APPENDIX F. EXPERIMENTAL SETUP





APPENDIX G. PULSE OXIMETER AND EAR CLIP

The following photographs show the pulse oximeter unit and ear clip sensor used in this experiment:



APPENDIX H. INDIVIDUAL SUBJECT TRENDS

The actual values (as opposed to % of BL1) for each subject are listed in the tables which follow.

BL1 = Baseline 1
STOP = STOPTIME (experimental endpoint)
BL2 = Baseline 2

VARIABLE: PULSE AREA

Subject	BL1	STOP	BL2	RATIO OF STOP/BL1	PRESYNCOPAL?
03	4.45	2.36	3.11	53.0%	NO
04	5.01	1.47	3.63	29.3%	NO
07	3.47	0.57	1.50	16.4%	NO
08	4.99	3.68	2.95	73.7%	NO
01	4.82	2.50	2.36	51.9%	YES
02	4.05	2.41	4.50	59.5%	YES
05	2.29	1.69	2.16	73.8%	YES
06	N/A	N/A	N/A	N/A	YES
09	3.26	0.93	2.46	28.5%	YES
10	3.8	2.52	9.05	66.3%	YES

VARIABLE: PULSE AMPLITUDE (volts)

Subject	BL1	STOP	BL2	RATIO OF STOP/BL1	PRESYNCOPAL?
03	.19	.10	.11	52.6%	NO
04	.14	.05	.09	35.7%	NO
07	.12	.02	.04	16.7%	NO
08	.15	.12	.09	80.0%	NO
01	.17	.09	.08	52.9%	YES
02	.15	.08	.12	53.3%	YES
05	.09	.06	.07	66.7%	YES
06	N/A	N/A	N/A	N/A	YES
09	.14	.05	.08	35.7%	YES
10	.17	.17	.29	00.0%	YES

APPENDIX H, CONTINUED:

VARIABLE: PULSE DURATION (msec)

Subject	BL1	STOP	BL2	RATIO OF STOP/BL1	PRESYNCOPAL?
03	530	460	540	86.8%	NO
04	800	630	840	78.8%	NO
07	630	500	670	79.4%	NO
08	770	590	640	76.6%	NO
01	520	490	590	94.2%	YES
02	600	530	710	88.3%	YES
05	510	600	660	117.6%	YES
06	N/A	N/A	N/A	N/A	YES
09	470	410	610	87.2%	YES
10	580	320	740	55.2%	YES

VARIABLE: SaO_2 (%)

Subject	BL1	STOP	BL2	RATIO OF STOP/BL1	PRESYNCOPAL?
03	96.9	96.9	96.9	100.0%	NO
04	99.8	99.8	99.8	100.0%	NO
07	97.6	94.9	97.9	97.2%	NO
08	99.8	99.8	99.8	100.0%	NO
01	99.8	89.8	99.8	90.0%	YES
02	99.8	98.8	99.8	99.0%	YES
05	99.8	88.8	99.8	89.0%	YES
06	N/A	N/A	N/A	N/A	YES
09	99.8	99.8	99.8	100.0%	YES
10	99.8	94.9	99.8	95.1%	YES

APPENDIX H, CONTINUED:

VARIABLE: TCD Mean Velocity (cm/sec)

Subject	BL1	STOP	BL2	RATIO OF STOP/BL1	PRESYNCOPAL?
03	40	32	42	80.0%	NO
04	46	46	46	100.0%	NO
07	50	36	42	72.0%	NO
08	50	42	42	84.0%	NO
01	44	30	36	68.2%	YES
02	50	36	50	72.0%	YES
05	50	26	56	52.0%	YES
06	46	30	44	65.2%	YES
09	58	42	58	72.4%	YES
10	46	26	46	56.5%	YES

VARIABLE: TCD Pulsatility Index

Subject	BL1	STOP	BL2	RATIO OF STOP/BL1	PRESYNCOPAL?
03	1.03	1.00	0.68	97.1%	NO
04	1.05	0.92	0.77	87.6%	NO
07	0.97	0.77	0.81	79.4%	NO
08	0.97	1.09	0.91	112.4%	NO
01	0.98	1.50	0.79	153.1%	YES
02	0.67	1.36	0.74	203.0%	YES
05	0.56	2.26	0.61	403.6%	YES
06	1.03	2.20	0.98	213.6%	YES
09	0.62	0.79	0.62	127.4%	YES
10	0.92	1.70	1.13	184.8%	YES

APPENDIX I. PERCENTAGE CHANGE AT ENDPOINT

VARIABLE	RATIO OF STOP/BL1: NON-PRESYNCOPAL GROUP	RATIO OF STOP/BL1: PRESYNCOPAL GROUP
PULSE AREA:	43.1%	56.0%
AMPLITUDE:	46.3%	61.7%
DURATION:	80.4%	88.5%
SaO2:	99.3%	94.6%
TCD MEAN: VELOCITY	84.0%	64.4%
PULSATILITY: INDEX	94.1%	214.2%

Notes: Values reflect overall mean for entire group.

BL1 = Baseline 1
STOP = STOPTIME (experimental endpoint)
BL2 = Baseline 2

N=4 for the non-presyncopal group
N=5 for the presyncopal group: AREA, AMPLITUDE, DURATION, SaO_2
N=6 for the presyncopal group: TCD MEAN VELOCITY, P.I.

Interpretation: A ratio (percentage) less than 100% indicates that the variable decreased at STOPTIME relative to BL1. A ratio (percentage) greater than 100% indicates that the variable increased at STOPTIME relative to BL1.

It is important to remember that the non-presyncopal group was still exposed to negative pressure, causing the associated physiological changes (blood pooling, etc.).

APPENDIX J. MEAN GROUP TRENDS (as % of BL1)

	NON-PRESYNCOPAL GROUP			PRESYNCOPAL GROUP		
VARIABLE	BL1	STOP	BL2	BL1	STOP	BL2
PULSE AREA:	100%	43.1%	61.2%	100%	56.0%	113.6%
s.d.:		25.4%	13.3%		17.4%	73.4%
AMPLITUDE:	100%	46.3%	53.9%	100%	61.7%	86.5%
s.d.:		26.9%	14.0%		24.0%	49.0%
DURATION:	100%	80.4%	99.1%	100%	88.5%	123.7%
s.d.:		4.4%	10.8%		22.3%	7.4%
SaO2:	100%	99.3%	100.1%	100%	94.6%	99.8%
s.d.:		1.4%	0.1%		5.0%	0.5%
TCD MEAN VELOCITY:	100%	84.0%	93.3%	100%	64.4%	98.2%
s.d.:		11.8%	10.9%		8.4%	9.7%
PULSATILITY INDEX:	100%	94.1%	79.2%	100%	214.2%	103.0%
s.d.:		14.2%	12.1%		98.1%	14.5%

Notes:
Each BL1 value is normalized to represent 100%.
Values at STOPTIME and BL2 are displayed as percent of BL1.
Each value is rounded to one digit after the decimal point.

BL1 = Baseline 1
STOP = STOPTIME (experimental endpoint)
BL2 = Baseline 2
s.d. = standard deviation for the associated value

For example: At STOPTIME, PULSE AREA for the non-presyncopal group decreased to 43.1% of the BL1 value, with a standard deviation of 25.4%.

N=4 for the non-presyncopal group
N=5 for the presyncopal group: AREA, AMPLITUDE, DURATION, SaO2
N=6 for the presyncopal group: TCD MEAN VELOCITY, P.I.

APPENDIX K. ACTUAL GROUP TRENDS

	NON-PRESYNCOPAL GROUP			PRESYNCOPAL GROUP		
VARIABLE	BL1	STOP	BL2	BL1	STOP	BL2
PULSE AREA:	4.48	2.02	2.80	3.64	2.01	4.10
AMPLITUDE: (volts)	0.15	0.07	0.08	0.14	0.09	0.13
DURATION: (msec)	682.5	545.0	672.5	536.0	470.0	662.0
SaO2: (%)	98.83	98.34	98.83	99.80	94.43	99.56
TCD MEAN: VELOCITY (cm/sec)	46.50	39.00	43.00	49.00	31.67	48.33
PULSATILITY: INDEX	1.01	0.95	0.79	0.80	1.64	0.81

Notes:

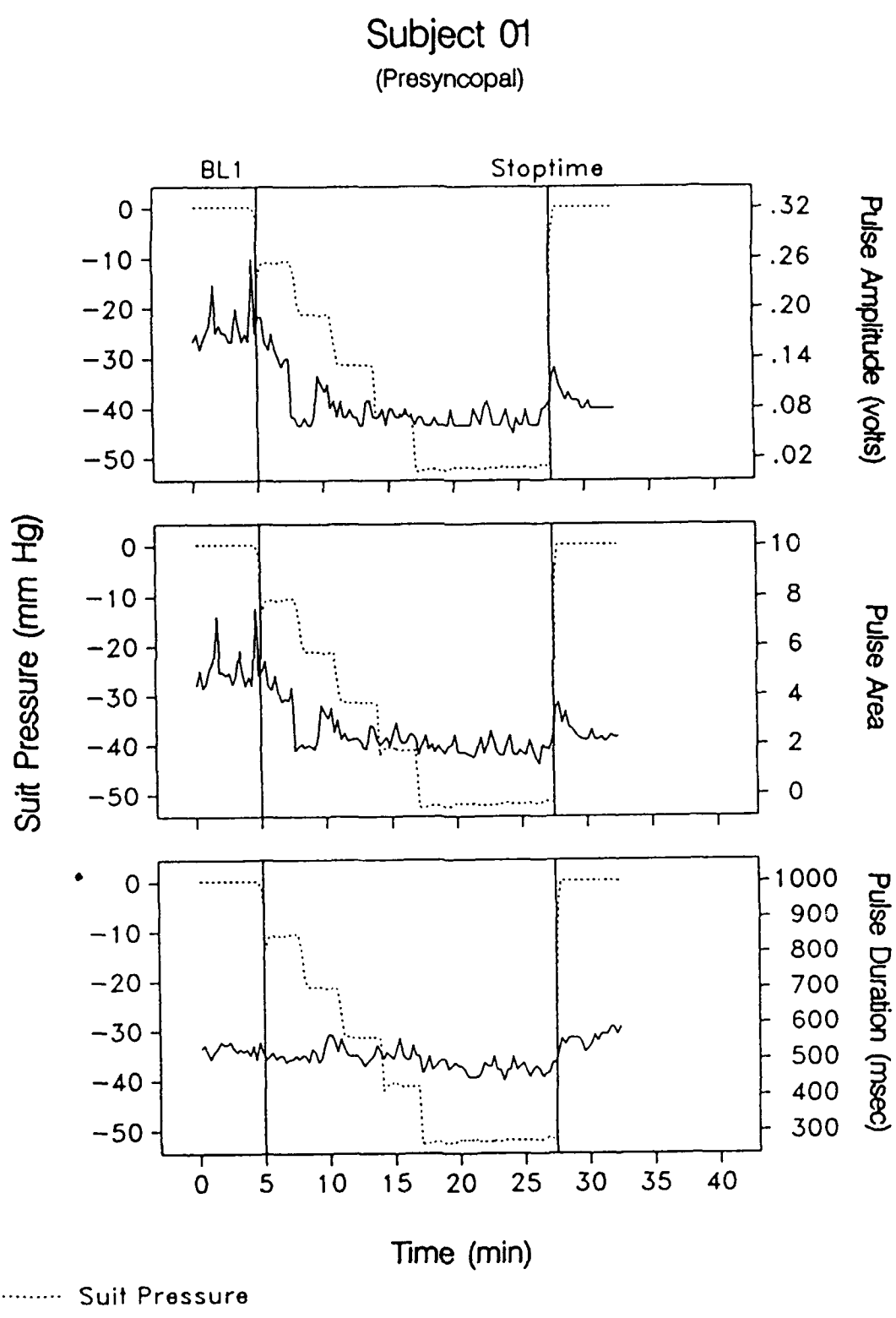
Each value in the chart represents the group mean for each variable, displayed as the actual value (not percentage). Each value is rounded to the indicated number of decimal places.

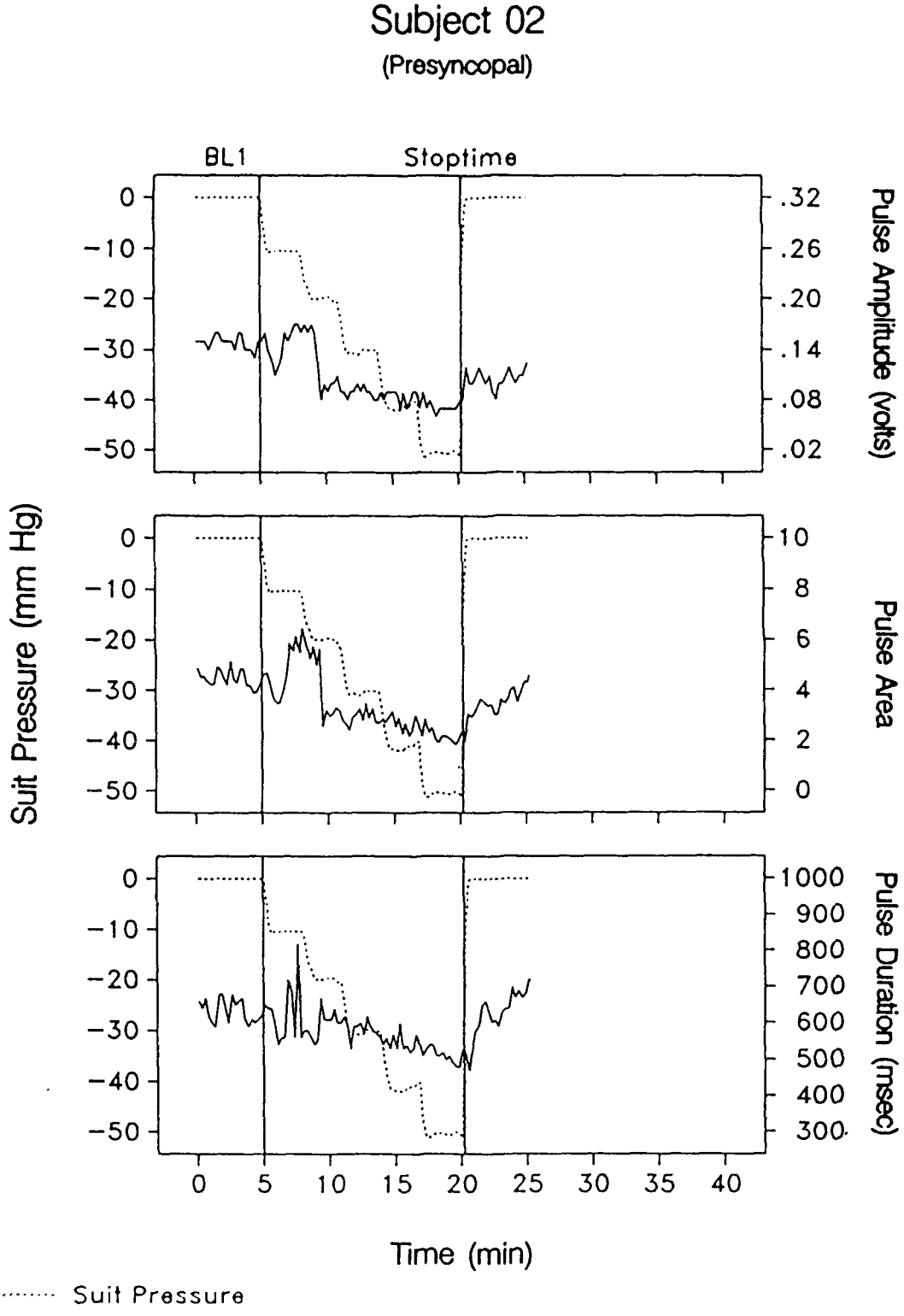
N=4 for the non-presyncopal group
N=5 for the presyncopal group: AREA, AMPLITUDE, DURATION, SaO_2
N=6 for the presyncopal group: TCD MEAN VELOCITY, P.I.

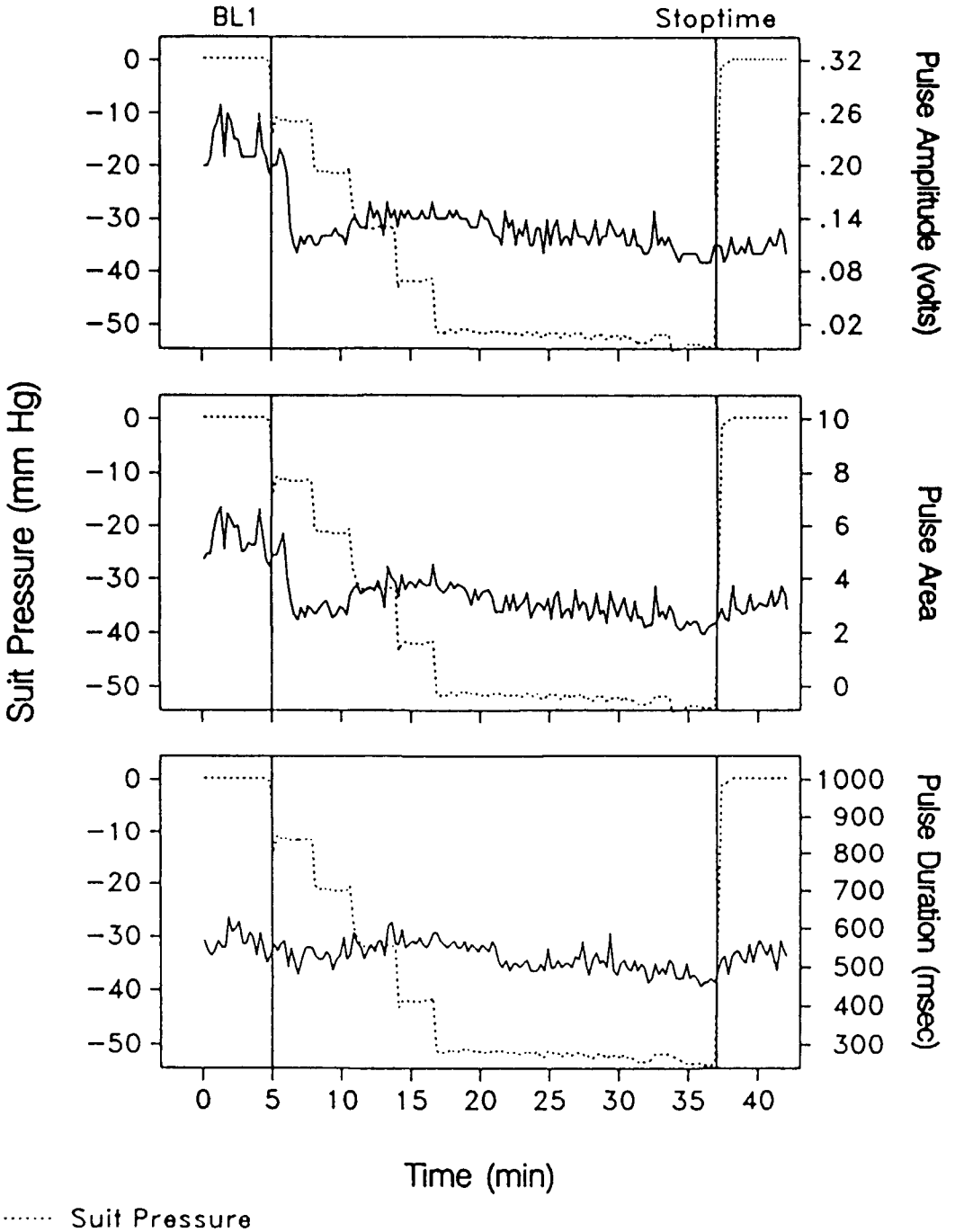
BL1 = Baseline 1
STOP = STOPTIME (experimental endpoint)
BL2 = Baseline 2

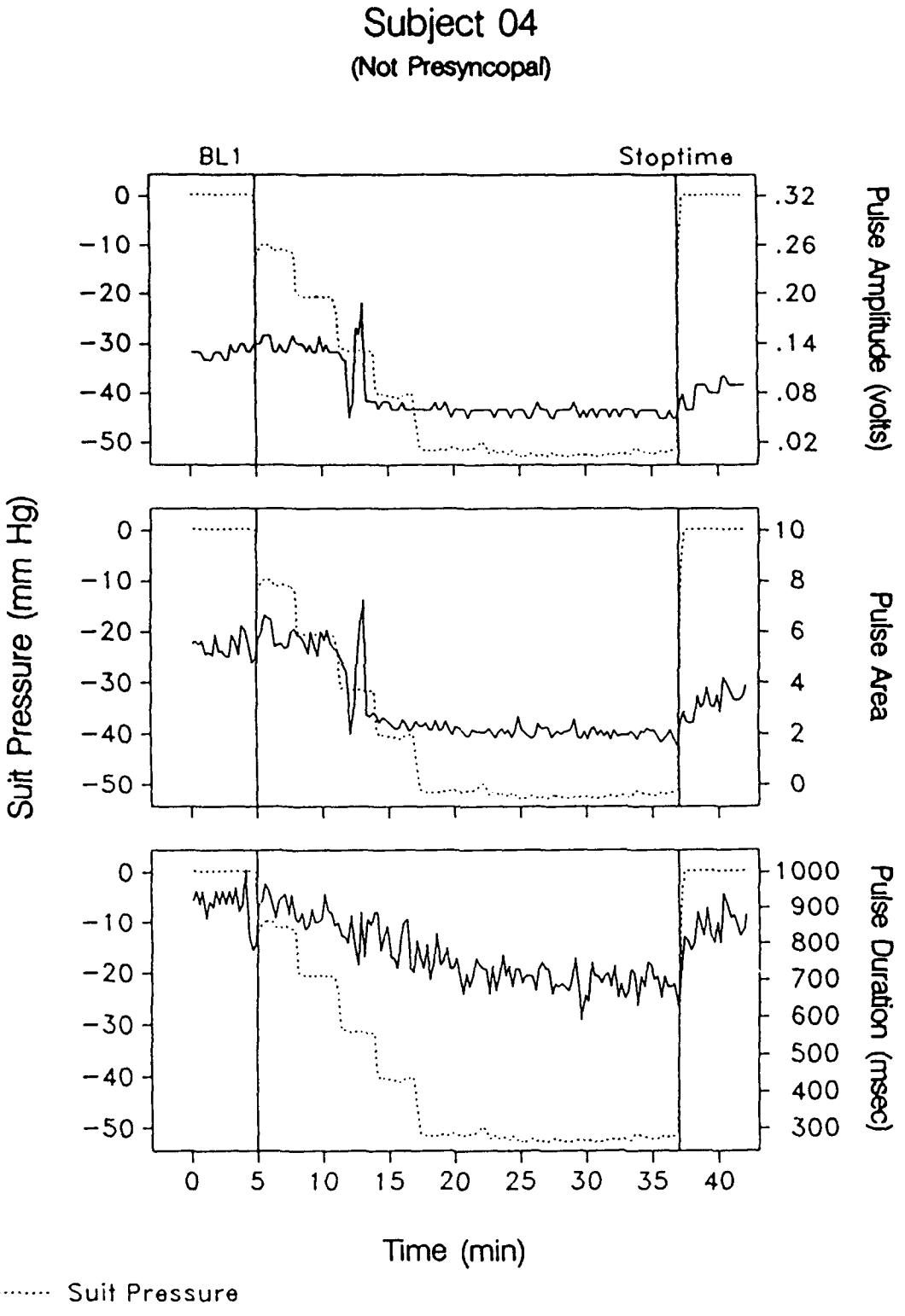
APPENDIX L. GRAPHS: PULSE AMPLITUDE, AREA, AND DURATION

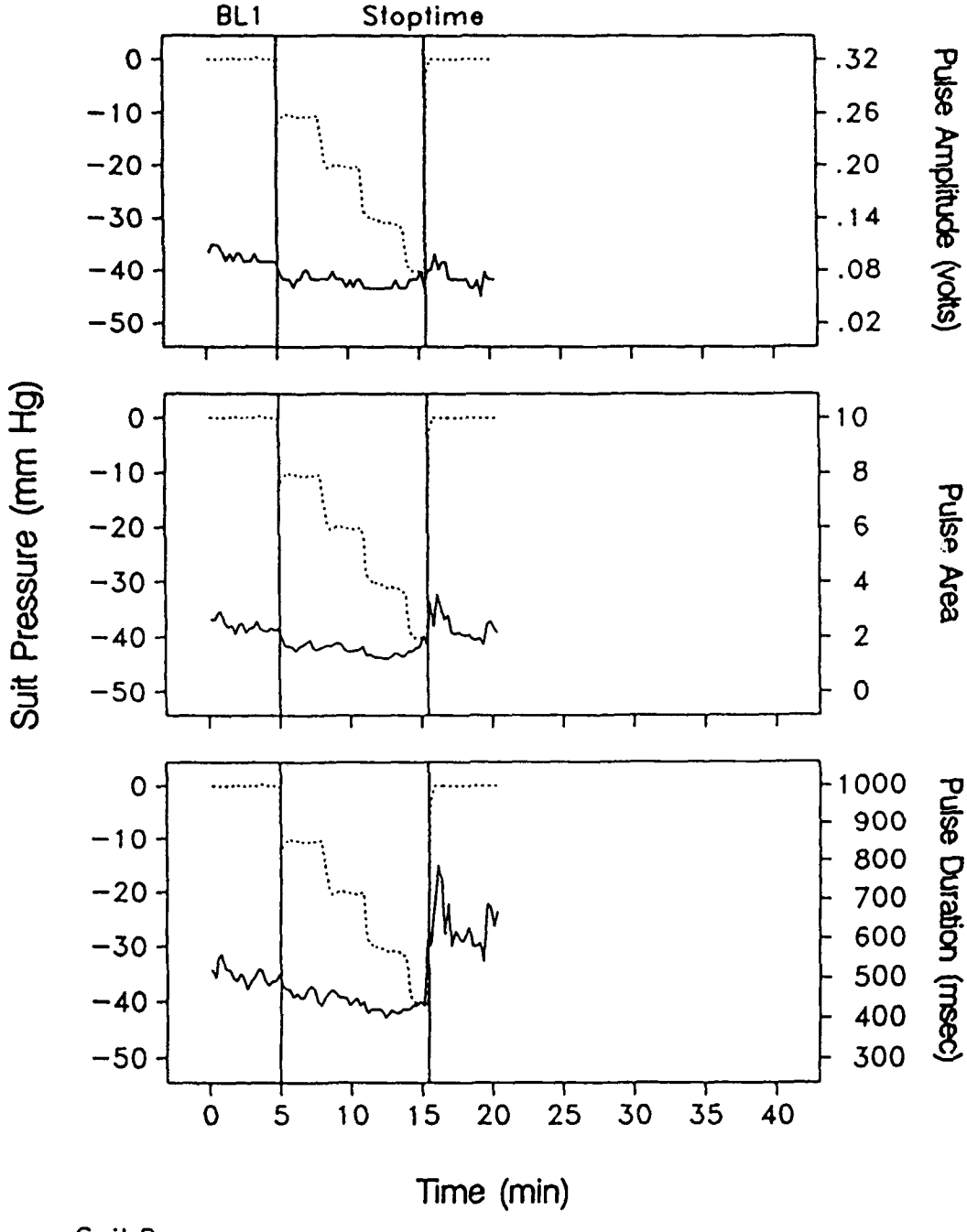
The graphs in this section demonstrate the gradual changes in Pulse Amplitude, Area, and Duration over the entire experimental profile for each subject. Because of the large amount of data obtained and occasional motion artifact, the median value of every 15 second segment was plotted. The median was chosen as a measure of central tendency because it is less sensitive to extreme values (for example, motion artifact) than the mean. TCD mean velocity, Pulsatility Index, and SaO_2 demonstrated relatively stable values or gradual changes until just prior to the endpoint and were shown in section IV, part D, entitled "Graphs: Two-Minute Window Around Endpoint".

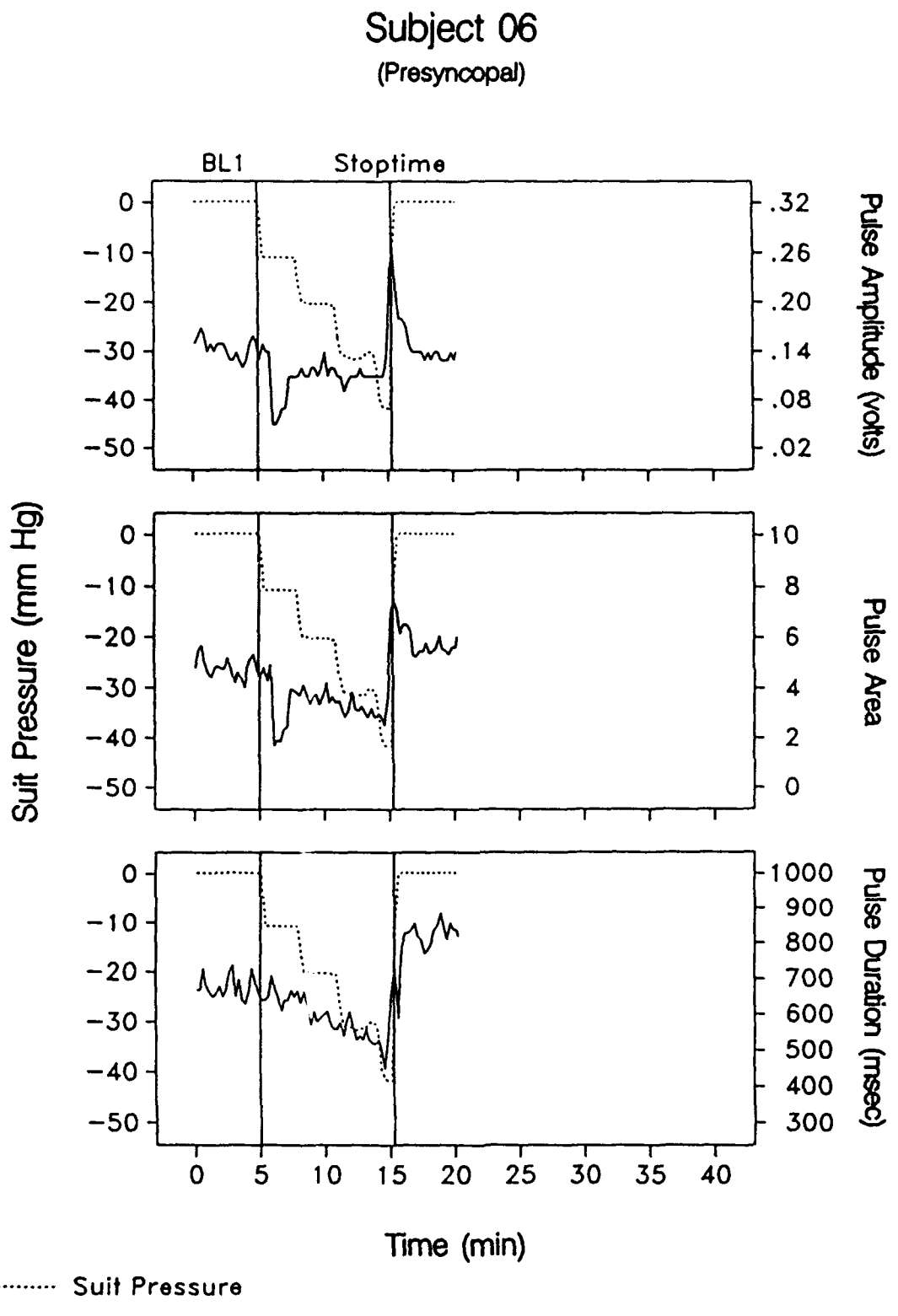

Subject 01
(Presyncopal)
BL1
Stoptime
Suit Pressure (mm Hg)
Pulse Amplitude (volts)
Pulse Area
Pulse Duration (msec)
Time (min)
Suit Pressure

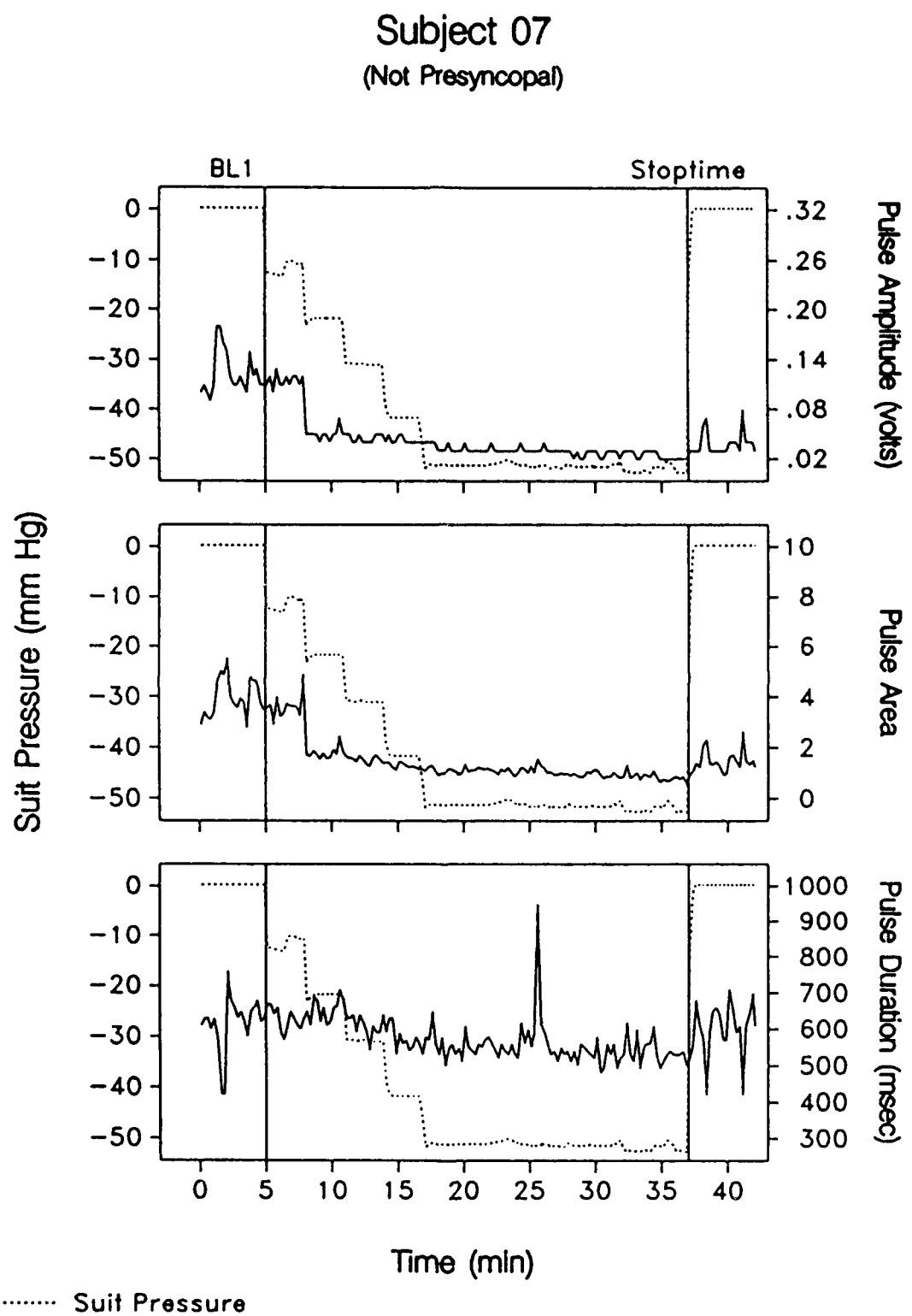

Subject 02
(Presyncopal)
BL1
Stoptime
Suit Pressure (mm Hg)
0
-10
-20
-30
-40
-50
.32
.26
.20
.14
.08
.02
Pulse Amplitude (volts)
10
8
6
4
2
0
Pulse Area
1000
900
800
700
600
500
400
300
Pulse Duration (msec)
0
5
10
15
20
25
30
35
40
Time (min)
Suit Pressure


Subject 03
(Not Presyncopal)
BL1
Stoptime
Suit Pressure (mm Hg)
Pulse Amplitude (volts)
Pulse Area
Pulse Duration (msec)
Time (min)
Suit Pressure


Subject 04
(Not Presyncopal)
BL1
Stoptime
Suit Pressure (mm Hg)
Pulse Amplitude (volts)
Pulse Area
Pulse Duration (msec)
Time (min)
Suit Pressure

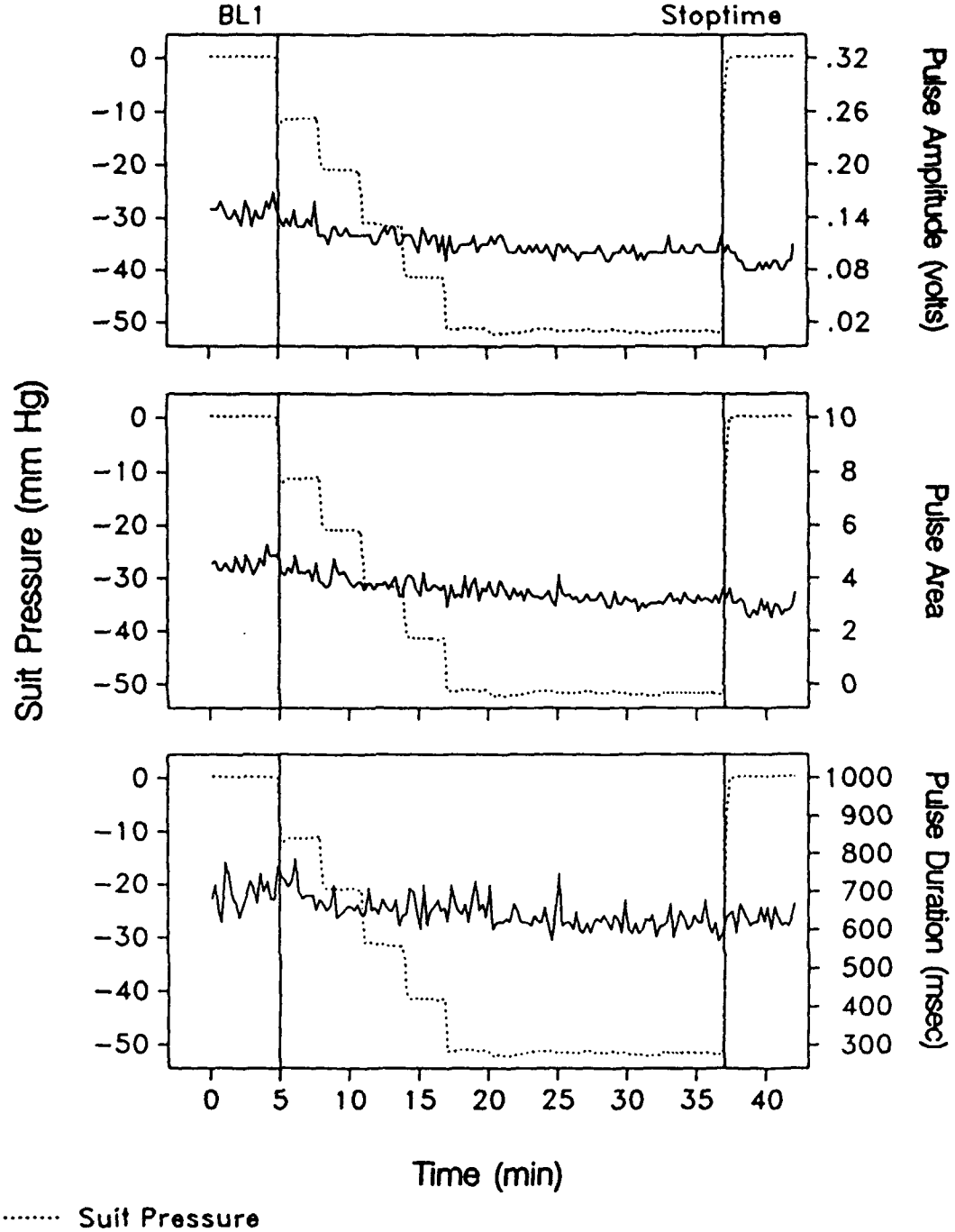

Subject 05
(Presyncopal)
BL1
Stoptime
Suit Pressure (mm Hg)
0
-10
-20
-30
-40
-50
.32
.26
.20
.14
.08
.02
Pulse Amplitude (volts)
10
8
6
4
2
0
Pulse Area
1000
900
800
700
600
500
400
300
Pulse Duration (msec)
0
5
10
15
20
25
30
35
40
Time (min)
Suit Pressure

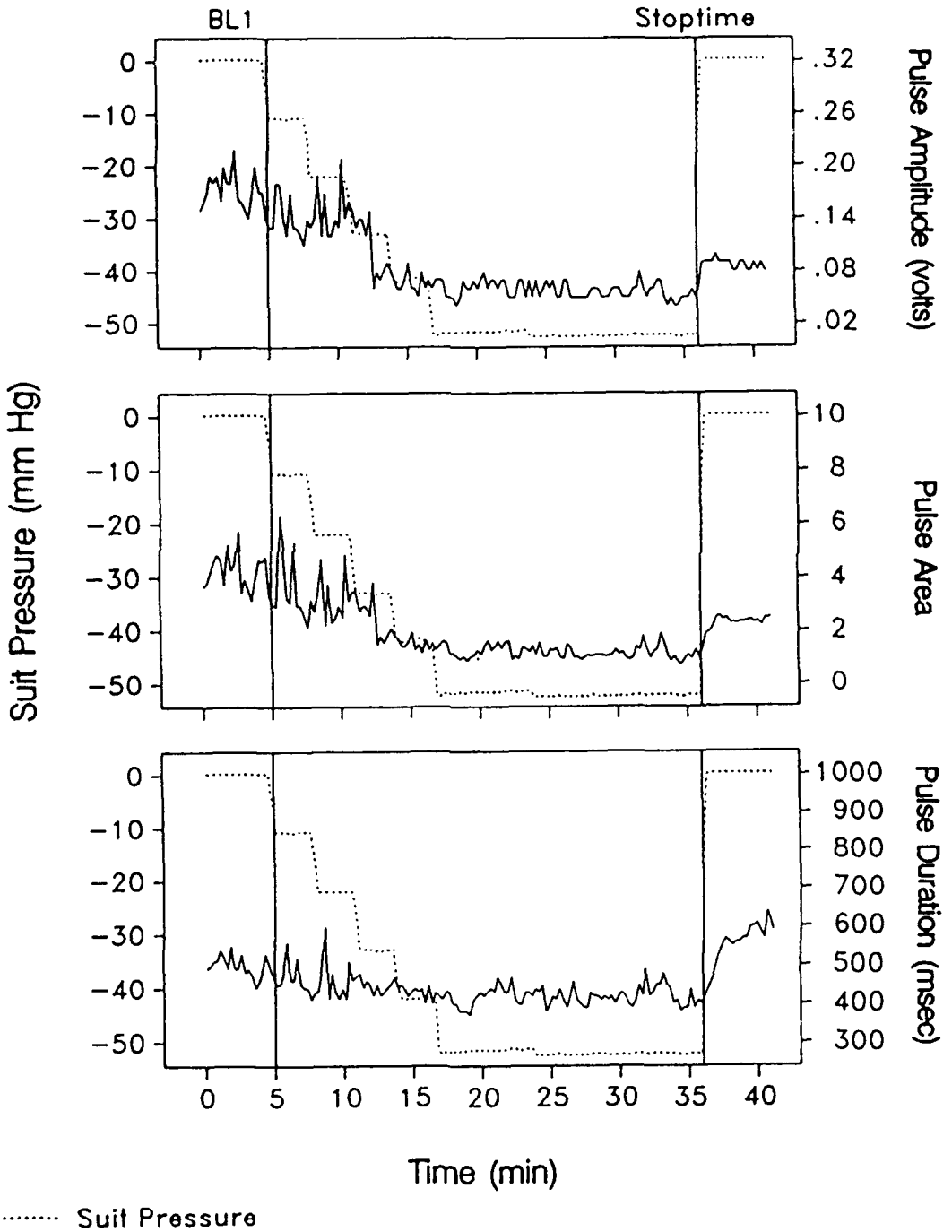

Subject 06
(Presyncopal)
BL1
Stoptime
Suit Pressure (mm Hg)
0
-10
-20
-30
-40
-50
.32
.26
.20
.14
.08
.02
Pulse Amplitude (volts)
10
8
6
4
2
0
Pulse Area
1000
900
800
700
600
500
400
300
Pulse Duration (msec)
0
5
10
15
20
25
30
35
40
Time (min)
Suit Pressure

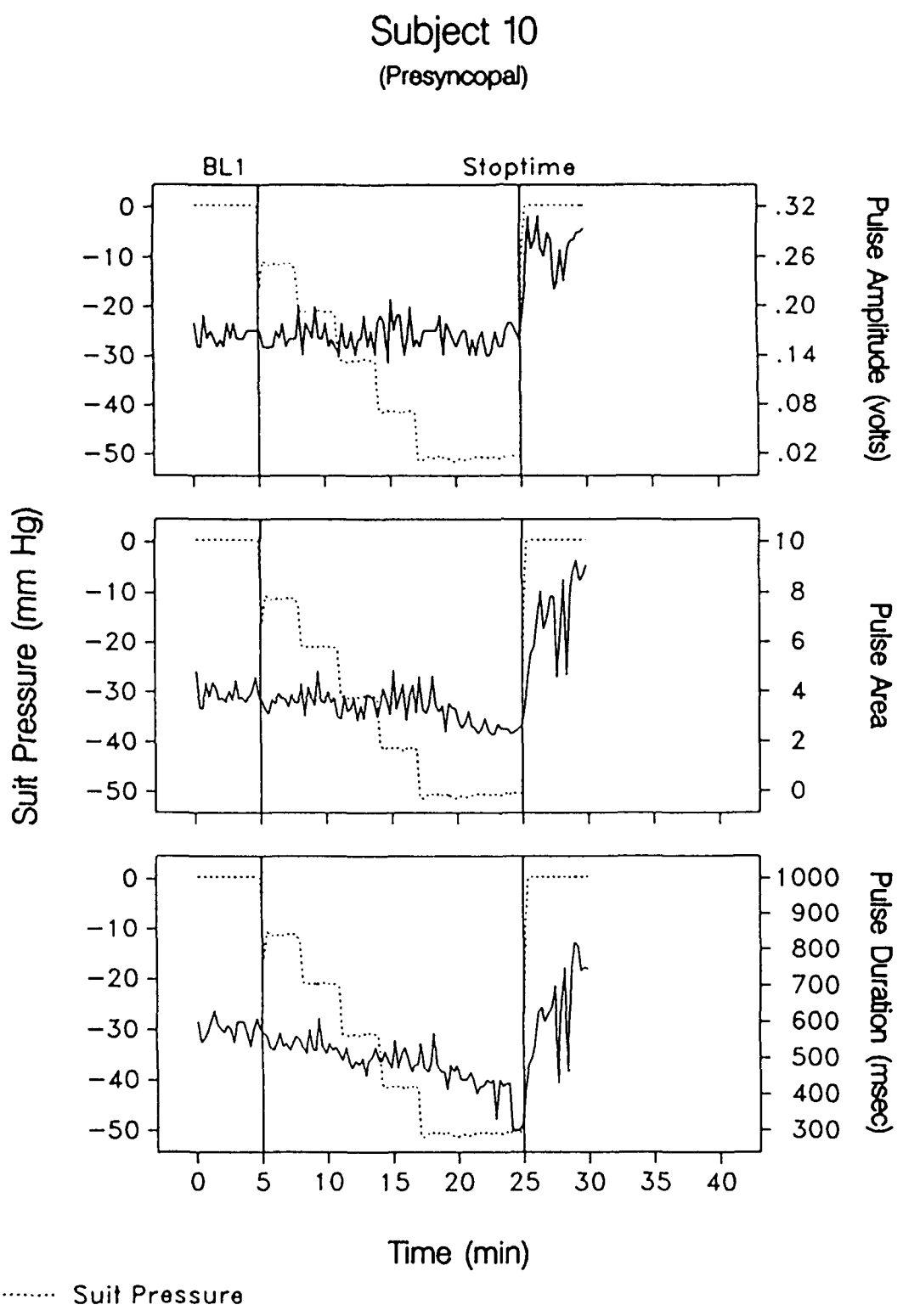

Subject 07
(Not Presyncopal)
BL1
Stoptime
Suit Pressure (mm Hg)
Pulse Amplitude (volts)
Pulse Area
Pulse Duration (msec)
Time (min)
Suit Pressure

Subject 08

(Not Presyncopal)




Subject 09
(Presyncopal)
BL1
Stoptime
Suit Pressure (mm Hg)
0
-10
-20
-30
-40
-50
.32
.26
.20
.14
.08
.02
Pulse Amplitude (volts)
10
8
6
4
2
0
Pulse Area
1000
900
800
700
600
500
400
300
Pulse Duration (msec)
0
5
10
15
20
25
30
35
40
Time (min)
Suit Pressure


Subject 10
(Presyncopal)
BL1
Stoptime
Suit Pressure (mm Hg)
Pulse Amplitude (volts)
Pulse Area
Pulse Duration (msec)
Time (min)
Suit Pressure

APPENDIX M. Erroneous Pulse Waveform Data from Subject 06:

Time	SaO2 %	Pressure	Area	Amplitude	
14:46	99.80	-41.70	3.13	0.12	
14:47	99.80	-41.70	2.88	0.11	<--- Normal
14:48	99.80	-41.70	3.47	0.10	<--- appearing
14:49	99.80	-41.70	3.11	0.13	<--- data
14:50	99.80	-42.00	3.11	0.13	
14:51	99.80	-41.70	3.61	0.13	
14:52	99.80	-41.70	3.65	0.14	
14:53	99.80	-41.70	3.80	0.13	
14:54	99.80	-41.70	4.09	0.13	
14:55	99.80	-41.70	3.47	0.13	
14:56	**99.80**	**-41.70**	**15.08**	**0.22**	**<--- Sudden**
14:57	**99.80**	**-41.70**	**8.97**	**0.12**	**<--- abnormal**
14:58	**99.80**	**-41.70**	**6.65**	**0.19**	**<--- increase**
14:59	**99.80**	**-41.70**	**6.15**	**0.20**	**<--- in**
15:00	**99.80**	**-41.70**	**5.85**	**0.20**	**<--- Area**
15:01	**99.80**	**-41.70**	**5.45**	**0.19**	**<--- and**
15:02	**99.80**	**-41.70**	**5.67**	**0.18**	**<--- Amplitude**
15:03	**99.80**	**-41.70**	**8.12**	**0.26**	**<---**
15:04	99.80	-41.70	6.06	0.22	<--- Explained
15:05	99.80	-41.40	7.36	0.20	<--- by
15:06	99.80	-42.00	8.05	0.28	<--- positional
15:07	99.80	-41.70	7.23	0.24	<--- change of
15:08	99.80	-41.40	5.99	0.24	<--- the pulse
15:09	99.80	-41.70	7.10	0.26	<--- oximeter
15:10	99.80	-41.40	6.90	0.26	<--- sensor.
15:11	99.80	-41.40	6.49	0.22	
15:12	99.80	-41.40	7.48	0.27	
15:13	99.80	-41.40	7.74	0.26	
15:14	99.80	-41.70	7.62	0.26	
15:15	99.80	-41.70	7.45	0.24	
15:16	99.80	-41.40	6.66	0.25	
15:17	**99.80**	**-41.10**	**8.40**	**0.31**	**<--- Actual**
15:18	99.80	-30.68	6.77	0.27	<--- Stop
15:19	99.80	-22.34	8.23	0.32	<--- Time
15:20	99.80	-16.98	8.11	0.32	<--- 15:17
15:21	99.80	-11.62	8.07	0.31	
15:22	99.80	-10.42	8.29	0.31	
15:23	99.80	-7.45	6.50	0.26	
15:24	99.80	-6.25	13.54	0.30	
15:25	99.80	-4.77	15.39	0.29	
15:26	98.83	-3.87	5.92	0.24	
15:27	98.83	-2.98	5.62	0.20	
15:28	98.83	-2.38	4.67	0.20	
15:29	98.83	-1.79	5.67	0.19	
15:30	98.83	-1.79	4.62	0.19	
15:31	98.83	-1.19	7.08	0.23	
15:32	98.83	-0.89	4.51	0.18	
15:33	98.83	-0.60	4.95	0.21	
15:34	99.80	-0.30	4.30	0.17	

APPENDIX N. TCD MEAN

	TIME	SaO2	VELOCITY	P.I.
WARNING INTERVAL IN SUBJECT 05	15:03	98.83 %	44 cm/sec	0.75
	15:04	98.83		
	15:05	98.83		
	15:06	98.83		
	15:07	98.83		
ACTUAL DATA SHOWN	15:08	98.83	40	0.71
FROM SUBJECT 05	15:09	98.83		
	15:10	98.83		
	15:11	98.83		
ONSET OF PI TREND-->	15:12	98.83	42	1.03
	15:13	98.83		
	15:14	98.83		
ONSET SaO2 TREND -->	15:15	97.85		
ONSET TCD TREND---->	15:16	96.88	30	1.41
	15:17	95.90		
	15:18	95.90		
	15:19	94.92		
	15:20	93.95		
	15:21	93.95	30	1.58
	15:22	92.97		
	15:23	91.75		
	15:24	90.77		
	15:25	89.79	26	2.26
	15:26	88.82		
ACTUAL STOPTIME----->	**15:27**	**88.82**		
	15:28	88.82		
MINIMUM MEAN VEL.-->	15:29	88.82	16	2.79
	15:30	88.82		
	15:31	88.82		
	15:32	88.82		
	15:33	88.82		
LOWEST SaO2,MAX PI->	15:34	87.84	36	6.19
	15:35	88.82		
	15:36	90.77		
	15:37	90.77		
	15:38	90.77	32	1.46
	15:39	91.75		
	15:40	93.95		
	15:41	93.95		
MEAN & PI RECOVERY->	15:42	93.95	44	0.86
	15:43	93.95		
	15:44	95.90		
	15:45	96.88		
	15:46	97.85		
	15:47	97.85	50	0.67
	15:48	97.85		
	15:49	97.85		
FULL SaO2 RECOVERY->	15:50	98.83		
	15:51	98.83	50	0.87

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